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PREFATORY NOTE

THE EDITORS have received so many enquiries concerning the typography and general format of the *Journal* that they take this opportunity of acknowledging their indebtedness to Mr. Carl Purington Rollins, Printer to Yale University, who selected the type and designed the *Journal* page. The face employed is Monotype Century Schoolbook No. 420, 10 point on 12 point for ordinary text, and 8 point on 9 point for small print, footnotes and bibliography. After the May issue of 1938 a special font of Century Schoolbook No. 420 type with long descenders was adopted. The type selected has enabled the *Journal* to give a readable five-inch line with an unusually high word count per page (550 to 580) without diminishing legibility or violating esthetic typography. The new front cover for the second volume was also designed by Mr. Rollins.

The *Journal* has somewhat modified its policies with regard to its free allowance for illustrations, a new statement of these matters being found on the inside of the front cover. Attention is also directed to the Style Book which is included at the end of the present number. This contains suggestions for the preparation of manuscripts for the *Journal*, and also an extensive alphabet of journals with official *World list* abbreviations opposite. These abbreviations represent the only consistent system so far available for the world literature of medicine and science. Separate copies of the Style Book are offered gratis to contributors and additional copies are supplied by the publishers or editors at a charge of 25 cents.

THE EDITORS wish also to express their warm appreciation to Mr. Thomas, the publisher, and to the George Banta Publishing Company, Menasha, Wisconsin, for their lively interest in everything pertaining to the welfare of the *Journal*. To the contributors and subscribers who have helped in the successful launching of the *Journal* THE EDITORS also extend their thanks.

ABERRANT GANGLION CELLS AS A SOURCE OF INTACT FIBERS IN SEVERED DORSAL ROOTS

DONALD DUNCAN AND E. S. CROCKER
Department of Anatomy, University of Texas, Galveston

(Received for publication September 30, 1938)

INTRODUCTION

IT IS BELIEVED that Toennies' (1938) confirmation of earlier investigations demonstrating the passage of nerve impulses centrifugally over the dorsal roots will stimulate further investigation of the histological aspects of the problem. For this reason, and because an explanation has been found for some of the previously published results, a brief report of a long series of experiments on the subject conducted in this laboratory is presented.

Past observation of the presence or absence of histologically efferent dorsal root fibers in mammals may be divided into three groups: (i) efferent fibers are numerous, Kuré and associates (see Kuré and Kajiyama, 1936), and Barron and Matthews (1935); (ii) efferent fibers are present but in small variable numbers, Kahr and Sheehan (1933), Okelberry (1935), and Young and Zuckerman (1937); (iii) efferent fibers are probably absent, Hinsey (1934). Each conclusion has been published repeatedly in the past and the literature on the subject may be found in Hinsey's thorough review. Papers of the first category have been convincingly explained and refuted by Storey, Hinsey *et al.* (1936) and by Young and Zuckerman. But the results of those finding a few intact fibers in the central stump after section have either been accepted as proof of intraspinal origin or explained away as due to some error in method. Neither explanation is adequate if the observations presented in this paper are correct; namely, intact fibers are found in varying small numbers in the central stumps of severed dorsal roots because they arise from aberrant ganglion cells that lie in the root between the point of section and the spinal cord.

Aberrant ganglia are mentioned in all the larger current text-books of gross anatomy and occasional original papers on the subject have appeared for many years. However, no mention of the aberrant cells as a source of intact fibers in the dorsal roots following section has been found. The one possible exception to this statement is a line by Hinsey to the effect that one preparation was discarded because it contained ganglion cells, but no further mention of them was made in his paper.

MATERIALS AND METHODS

Experimental section of lumbo-sacral dorsal roots was performed on 35 cats. The operations varied from section of a single rootlet near the spinal cord to extradural section of the second lumbar to the second sacral dorsal roots of one side. The operations included 9 attempts to isolate single rootlets by section of the adjacent ones, above and below. In all cases the central stump was fixed in 1 per cent osmic acid and the distal stump, the ganglion, and the trunk of the affected root, as well as the adjacent uninjured roots were fixed and stained according to Marchi's method. All material was examined in carefully teased preparations. Subsequently 8 of the largest lumbar roots from 2 cats were cut in

serial longitudinal sections, stained with thionin and each section was carefully examined for nerve cells. Lower lumbar roots from 2 normal dogs and 2 dogs subjected to dorsal root section were similarly examined for nerve cells. In both of the operated dogs lower lumbar roots were sectioned extradurally. In one case the animal lived 21 days after section and in the other 30 days. Ten lumbar roots from 3 normal dogs were stained in bulk with carmine and then teased and examined for the presence of extra-ganglionic nerve cells.

Results

It is considered unnecessary to report the results from the 35 cats in detail. With a minor exception they were in complete agreement with Hinsey's previous results and conclusions for the same species. The slight exception noted to Hinsey's results was the persistent finding of occasional normal fibers in the central stump and degenerating fibers in the distal stump.

Table 1. Incidence of aberrant cells in lumbar dorsal roots

Animal	Root examined	Extradural cells	Intradural cells
Cat 9–38	R. & L. 7L		0
Cat 10–38	R. & L. 5, 6, 7L		10
Dog 1–38	L5L	16	0
	L6L	10	0
	L7L	6	0
Dog 2–38	R7L	41	
	L7L	134	97
Dog 4–38	R6L*	39	
	R7L*	208	
Dog 5–38	L6L*	12	Numerous in
	R7L	111	teased roots of
	L1S*	227	L6L & L1S

* These roots were divided 5 mm. from their ganglia 21 days (Dog 4) and 30 days (Dog 5) before sacrifice.

Such fibers were always few in number and were found in about one half of all preparations. It was not until after 25 cats had been operated upon and examined that a satisfactory explanation for the occurrence of these occasional apparently efferent fibers was discovered. At this time ganglion cells with attached intact fibers were observed in the central stump of a dorsal root that had been cut intradurally about halfway between the ganglion and the spinal cord (Fig. 1 and 2). The results of the additional work performed to extend and confirm the observation are described in the succeeding paragraphs.

The numerical results of a search for nerve cells in the dorsal roots are recorded in Table 1. As indicated in the table such cells are rare in the cat and much more numerous in the dog. A similar difference was recorded by Peters (1935) for aberrant cells in the sensory root of the trigeminal nerve. In addition to cells recorded in the table, aberrant cells were found in the

teased preparations of the central ends of the cut dorsal roots in 4 instances out of 30 cat specimens examined for this feature. Since the entire root could not be examined in these cases, and since an occasional normal fiber was found in 15 of these preparations, it is believed that serial sections of the entire roots would have revealed enough additional cells to account for the intact fibers. An undetermined number of aberrant cells were also seen in each of 10 lumbar dorsal roots from 3 dogs. These roots had been stained in bulk with carmine and teased out in glycerine. It was considered that a sufficient number of specimens from the dog had thus been examined to establish the constant occurrence of aberrant dorsal root ganglion cells in this species.

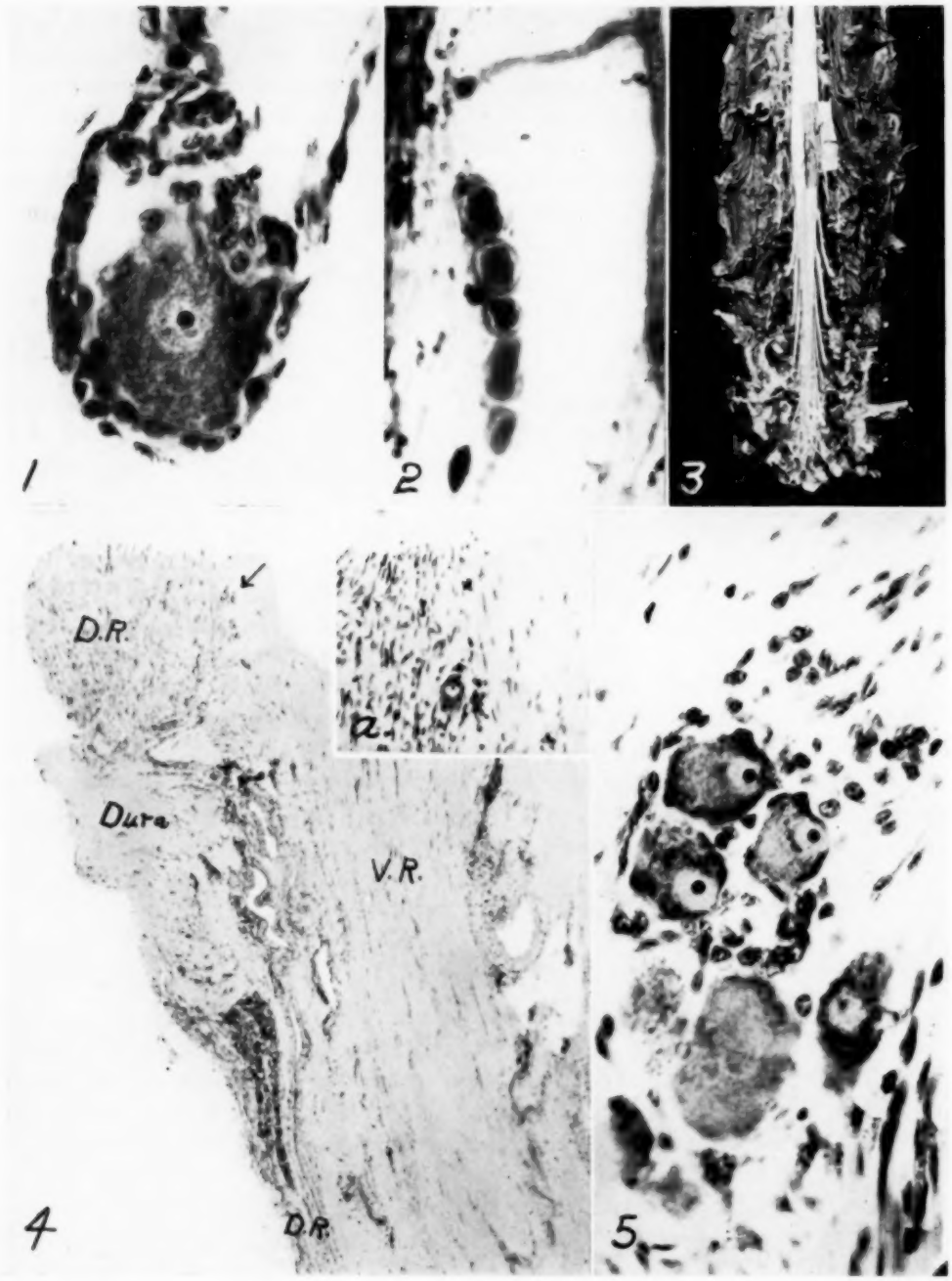
Conditions in the dog are somewhat different from those in the cat, not only in regard to the number but also the location of the cells. In the dog the extradural portions of the lumbo-sacral roots are long as compared to the more common arrangement in man, rat, rabbit, and cat. This meningeal relation in the dog has been illustrated by Papez (1929, p. 137), but is considered of sufficient importance to investigators to be noted again, (Fig. 3). Most of the aberrant cells are found in the long extradural portion of the root, but intradural cells are much more common in the dog than in the cat. The largest collections of aberrant cells occur just outside the dura (Fig. 4). Single cells are fairly numerous throughout the entire extent of each root examined.

Survival of these cells and their processes following dorsal root section was easily demonstrated in the dogs following operation. The cells shown in Fig. 4 are from a root divided peripheral to these cells. Teased osmium treated preparations of the intradural portion of this root contained numerous normal fibers of all calibers and additional ganglion cells as well. Many of the aberrant cells in the divided roots exhibited typical retrograde changes (Fig. 5). According to Hinsey, Krupp, and Lhamon (1937) this indicates that the peripheral processes, rather than the central, were cut.

Discussion

Although Barron and Matthews stated that as many as 32 per cent of the fibers of the dorsal roots of the cat failed to degenerate following separation from the ganglia, careful repetition of their procedures failed to establish anything contrary to the previous conclusions of Hinsey which have been subsequently restated by Storey, Corbin, and Hinsey. The occasional normal fibers found in the cat are so few in number and so readily accounted for by the presence of a like incidence of aberrant cells, that they must be considered as a minor exception to the complete degeneration that takes place in the central end of the severed dorsal root in this animal.

In the dog, nerve cells in the roots are sufficient in number to be a considerable source of confusion. Their incidence is great enough to account for Okelberry's (1935) convincing demonstration of intact fibers in the severed dorsal roots of this animal. Okelberry's results have been dismissed by several writers on the basis of the difficulty of cutting the roots extradurally with-



All figures are unretouched photographs taken under the magnification indicated for each figure.

FIG. 1. An aberrant dorsal root ganglion cell found in the left seventh lumbar root of cat 10–38. ×460.

FIG. 2. Aberrant ganglion cells in a teased preparation of the central end of a lumbar dorsal root which had been divided 21 days before fixation, from cat 4–37. ×135.

(*Continued next page*)

out involvement of the ganglion. They point to the lesser number of fibers found after intradural section as proof of this contention. Such criticism of Okelberry's results is entirely unjustifiable because of the ease of extradural section in the dog. Even if the lumbar roots were sectioned as much as an inch away from the ganglion in this animal, fairly numerous normal fibers would usually be found in the intradural portions of the roots involved. It is believed that any careful repetition of Okelberry's work would completely substantiate his findings, but that such results are to be accounted for almost if not entirely on the basis of extra-ganglionic cells in the roots and not by assuming that the remaining intact fibers arise from the cord. The results obtained by Young and Zuckerman on the monkey cannot be due entirely to the presence of aberrant cells, but their claims of an appreciable number of fine myelinated efferent fibers in the monkey should be viewed with caution because of the great difficulty of distinguishing normal fibers from unfragmented segments of fibers undergoing degeneration. This is especially true of the myelinated fibers of fine caliber studied in cross sections.

As mentioned in the introduction, nerve cells in the dorsal roots as aberrant ganglia have been described repeatedly in the past and statements concerning them may be found in the current editions of texts of Cunningham, Gray, Morris, and Piersol. The occurrence of these cells as isolated and scattered elements has been mentioned most recently by Tarlov (1937). The earlier papers on aberrant cells are cited by Tarlov and by Peters.

Summary and Conclusions

Experimental section of the lumbo-sacral dorsal roots was performed on 35 cats and 2 dogs. After an interval for degeneration occasional normal myelinated fibers were seen in the central ends of the severed roots from 15 of the cats and fairly numerous normal fibers were seen in the central stumps from both dogs.

Aberrant dorsal root ganglion cells were found in the central ends of the cut dorsal roots from 4 of the cats and both dogs. The qualitative presence of aberrant cells in each of 10 normal roots from 3 dogs was established.

Serial sections of lumbo-sacral dorsal roots from 2 normal cats and 4 dogs, 2 normals and 2 operated, were examined and the number of aberrant cells was determined.

In the cat the number of aberrant cells is small, some roots containing

FIG. 3. A dissection of the lower lumbar and sacral roots of a young adult police dog; Close examination of the figure will show that approximately one half of the length of any of these roots is extradural. ×½.

FIG. 4. A section from dog 5–38 showing a normal ventral root, V. R., and portions of a severed dorsal root, D. R., at the point where these roots pass through the dura. A small collection of ganglion cells is shown in the extradural portion of the dorsal root. These cells are at least an inch central to the main ganglion. ×45. Insert "a" shows the single intradural cell indicated by the arrow on the main figure at a higher magnification. ×135.

FIG. 5. Aberrant cells from dog 4–38 showing eccentric nuclei and chromatolysis in a dorsal root severed 21 days before fixation. ×460.

none at all and not more than 6 were seen in any one root. A total of 10 were seen in the 8 roots examined in serial section. In the dog the cells are much more numerous, and no root was examined that did not contain some of them. Most of these cells are found in the long extradural portion of the root, but they are also found in smaller numbers intradurally. In the 10 roots completely examined, the number of cells in the extradural portion varied from 6 to 227.

These cells and their processes survive section of the roots and are believed to account for the so-called efferent fibers that have been demonstrated in otherwise adequately controlled experiments.

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THE LOCALIZATION IN THE BRAIN STEM OF THE OESTROUS RESPONSES OF THE FEMALE GUINEA PIG[1]

EDWARD W. DEMPSEY[2] AND DAVID McK. RIOCH
From the Department of Anatomy, Harvard Medical School, Boston

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IT HAS BEEN shown previously that a well-defined pattern of reflex behavior of the female guinea pig begins suddenly at oestrus and persists for a definite period (Young, Myers and Dempsey, 1935). This reflex pattern is elicited by rubbing or touching the hair and skin on the dorsal lumbar and perineal regions, or by the sexual behavior of the male. The pattern is characterized by opisthotonus, an elevation of the pelvis, a dilatation of the vulvar regions, and it is frequently accompanied by a guttural, purring vocalization. The close relation of this behavior to the endocrine events of the reproductive cycle has been demonstrated by its synchronization with the pre-ovulatory changes in the Graafian follicles (Myers, Young and Dempsey, 1936), and by the ease with which it can be produced experimentally by appropriate hormone injections (Dempsey, Hertz and Young, 1936).

The desirability of determining the neural mechanism responsible for the control of oestrous behavior immediately became apparent after the establishment of the facts mentioned above. Bard and Rioch (1937) and Brooks (1937) have demonstrated, for the cat and rabbit respectively, that oestrous behavior can occur in animals which have been completely deprived of the neocortex. It seemed desirable, therefore, to learn more about the nervous elements involved in sexual behavior. The present paper represents a series of experiments which have been designed to determine the approximate localization in the brain stem and spinal cord of these reflex mechanisms.

MATERIALS AND METHODS

Brain lesions of varying extent were produced surgically in ovariectomized guinea pigs. Following the operative procedures, suitably timed injections of oestrin and progesterone were made, as it has been shown previously that such hormonal treatment in spayed females is invariably followed by oestrous behavior (Dempsey, Hertz and Young, 1936). Whenever possible, chronically operated animals were maintained for considerable periods of time and tested for sexual receptivity after repeated injections of the hormones. However, many of the individuals in which large lesions had been produced, particularly lesions involving bilateral destruction of the motor cortex, refused to eat after the operation and became moribund within a few days. With these animals it was necessary to resort to subacute procedures, and the injections and tests for sexual behavior were carried out immediately after the operation, while the general condition of the animal was still good.

The tissue to be removed was either cut out under anesthesia with a sharp spatula or sucked out through a fine glass tube attached to a suction pump.

At the sacrifice of each animal, the brain was removed and fixed in 10

[1] This work was supported by a grant from the Ella Sachs Plotz Foundation.
[2] National Research Council Fellow in the Natural Sciences.

per cent formalin. Gross dissection was employed in the case of several specimens to determine the extent of the lesion, while in other specimens serial sections 35 μ in thickness were prepared and stained in thionin. In addition to the lesions produced in ovariectomized guinea pigs, transection of the brain stem at three different levels was performed in an acute experiment in an oestrous female cat. This experiment, which was undertaken in collaboration with Dr. Robert S. Morison of the Department of Physiology, has provided information similar to that arising from the guinea pig experiments, and is therefore included in this report.

Experimental

Cortical and striatal lesions

Chronic survival experiments. At the beginning, attempts were made to prepare chronic ovariectomized, decorticate guinea pigs by a three-stage

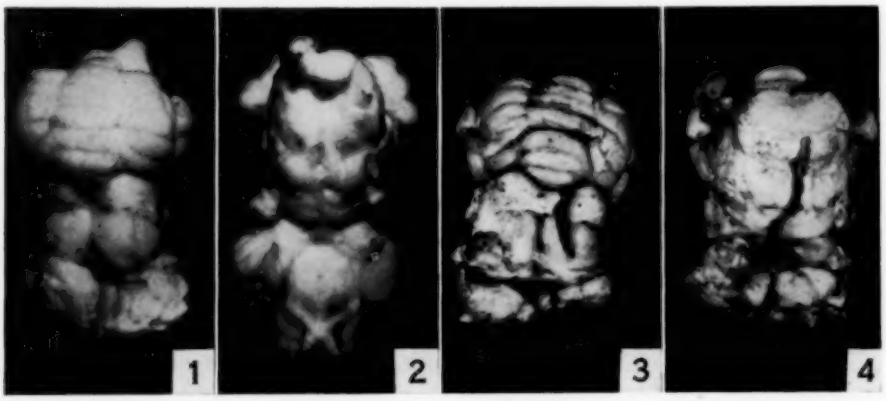


Fig. 1 and 2. Dorsal and ventral views of the brain of a decorticate guinea pig which came into heat following injections of oestrin and progesterone. Sections through the brain of this animal are shown in Fig. 6, 7 and 8.

Fig. 3 and 4. Dorsal and ventral views of the brain of a guinea pig in which acute decortication was performed. Oestrous responses were obtained after the first transection, not after the second.

operative procedure. It rapidly became evident, however, that even hemidecortication is often followed by death because of refusal of the animal to eat. Forced feeding was undertaken postoperatively with only slight prolongation of life, since it was impossible to supply the large quantity of food which normally is consumed by these rodents. Nevertheless, 9 animals survived hemidecortication for varying periods of time. These individuals were injected with 100 I. U. oestrin (Progynon-B, Schering)[2] daily for two days, and 0.1 I. U. progesterone (Proluton, Schering) was administered 48 hours after the first injection of oestrin. Six of the 9 females came into full behavioral

[2] The hormone preparations used in this work were supplied through the courtesy of Dr. Erwin Schwenk of the Schering Corporation.

oestrus within the usual latent period of 3 to 7 hours after the progesterone injection. Completely normal reflex responses were obtained, and no difference was observed on the two sides of the animals with regard to the threshold of stimulation necessary to elicit the response.

Acute terminal experiments. Since the preparation of chronic, surviving decorticate animals was not feasible, an attempt was made to induce oestrous behavior in animals in which the cortex was removed acutely (Fig. 1 and 2). Four animals were injected with 250 I. U. oestrin and 24–36 hours later the cortex and other portions of the forebrain were bilaterally ablated under ether anesthesia. Forty-eight hours after the injection of oestrin, 0.1 I. U. progesterone was administered and oestrous responses were demonstrable in two of the four preparations 4 and 5 hours respectively after the progesterone injection. The responses in these animals were unmistakable, and were accompanied in one instance by the purring vocalization which is often elicited with the oestrous response in normal animals. Although completely normal in all respects, the responses elicited from these two animals were easily fatigued. Only two or three responses could be evoked in quick succession, after which a period of 10 to 15 minutes' rest was necessary before the response again appeared on stimulation, although in normal animals 20 or 30 responses may be obtained easily in rapid succession.

Histological examination of the brains of these animals showed that the neocortex and hippocampus had been completely removed in both instances. In both animals considerable damage had also been done to the caudate-putamen, only a few of the most medially located cells remaining in one case (Fig. 6, 7 and 8), while in the other animal the medial half of the complex remained on the right side and had been completely removed on the left. The olfactory stalks had been completely severed in one animal, while in the other they remained intact.

Medial and basilar forebrain lesions

Chronic survival experiments. Lesions were produced by means of a small sucker in the septal regions in 9 animals, involving the septal nuclei, the anterior commissure, the fornix and the medial half of the tuberculum olfactorium (Fig. 9, 10 and 11). After recovery from the operation, these animals were injected with oestrin and progesterone, and sexual behavior occurred in 8 cases. No difference in the stimulation threshold of the reflex could be noted on the two sides of any animal, although examination of the brains of these individuals showed that the lesion was not symmetrical in all cases, and in some instances structures on only one side had been destroyed.

Similar but more extensive lesions involving the pre-optic and anterior hypothalamic areas were also made, but in no case was oestrous behavior observed when oestrin and progesterone were injected. However, these animals rapidly became cachectic and showed such disturbances in water metabolism and heat regulation that their failure to show oestrous responses could well be attributed to general systemic effects.

Acute terminal experiments. Sexual behavior was observed in an acute experiment in which the anterior hypothalamus had been removed. An ovariectomized guinea pig was injected with oestrin and progesterone, and immediately following the injection of progesterone the brain stem was transsected at a level just anterior to the mammillary bodies (Fig. 3 and 4). Seven hours later, unmistakable oestrous reflexes were observed when the lumbar and perineal regions of the animal were stimulated. A second cut was then made at a level just anterior to the superior colliculus and just behind the mammillary bodies, after which no further responses referable to oestrous behavior were obtained (Fig. 5).

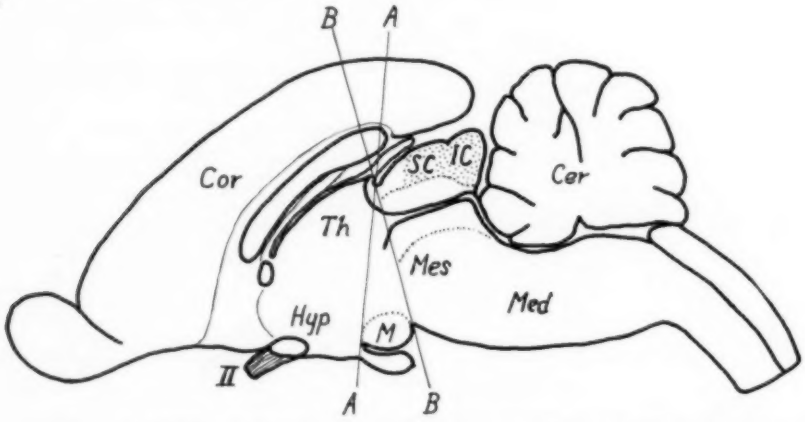


FIG. 5. Diagram of medial sagittal section through brain of guinea pig. Cor—cortex, Th—thalamus, Hyp—hypothalamus, M—mammillary body, SC—superior colliculus, IC—inferior colliculus, Mes—mesencephalon, Med—medulla, Cer—cerebellum, II—optic nerve. Oestrous responses were obtained after transection along plane AA but were abolished by transection along plane BB. Lesions in the optic tectum shown by the stippled area also abolish oestrous responses.

Results similar to those described in the preceding paragraph were also obtained in an acute experiment in an oestrous cat. On the third day following an intramuscular injection of 10,000 I. U. oestrin, well-marked oestrous responses were observed. These responses were elicited by manual stimulation of the perineal regions, and consisted of growling, crouching with the forefeet and active treading with the hindlegs. Upon cessation of stimulation, the cat lay on her side and repeatedly rubbed her cheek and occiput against the floor.

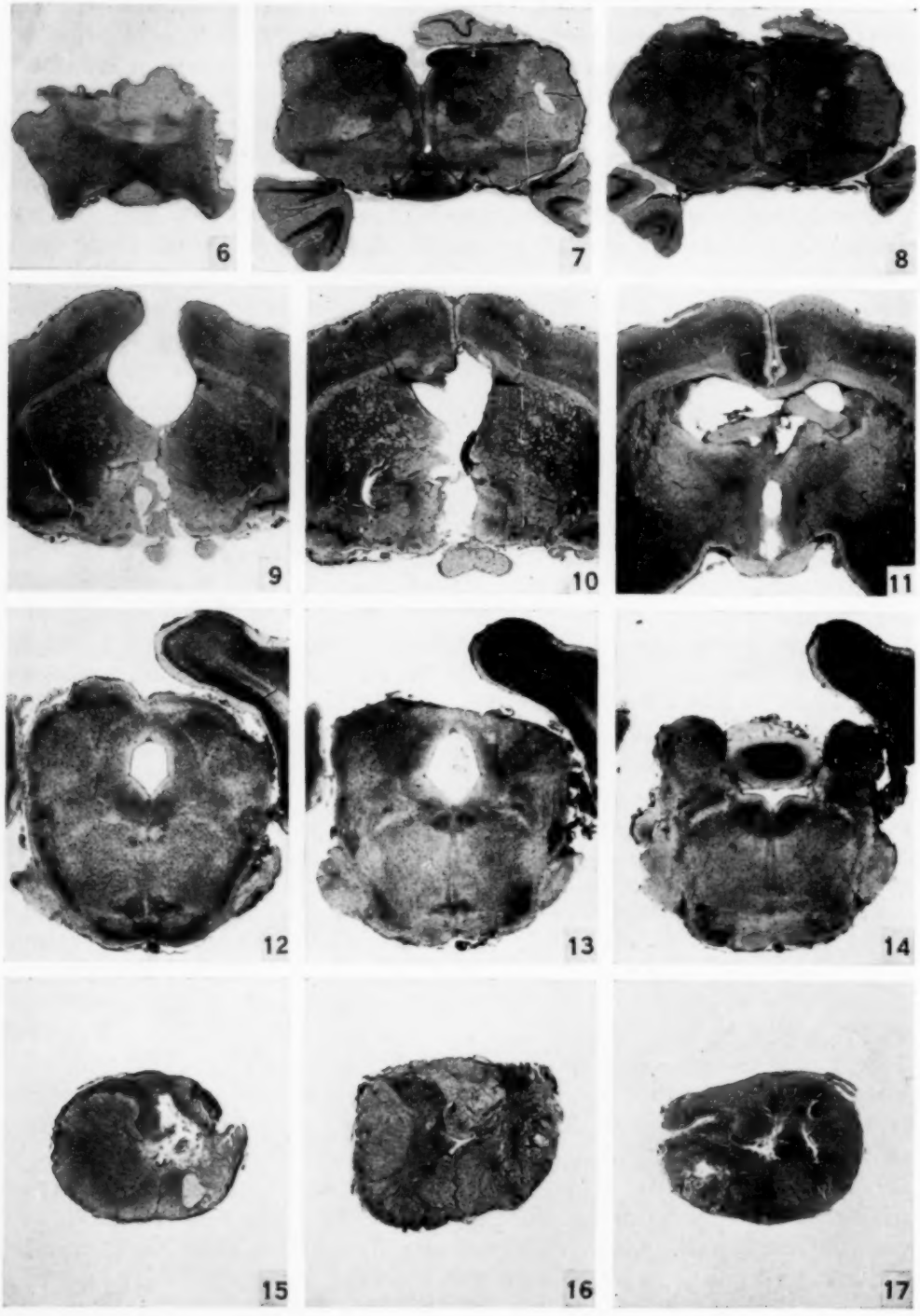
Under ether anesthesia a tracheal cannula was inserted, the skull opened, and decortication performed by a sloping transection of the brain stem from a point 2 to 3 mm. rostral to the superior colliculi to a point just rostral to the optic chiasm. All brain tissue anterior to the cut was removed, the hemorrhage controlled, and the animal placed on the floor to recover from the anesthesia. An hour later, manual stimulation of the external genitalia was followed by shortening of the long back muscles and extension of the hindlegs. When supported on all four feet, stimulation of the genitalia caused an elevation and rotation of the pelvis, flexion of the front legs, and extension of the

hind legs with the result that the cat assumed a crouching posture with the hind legs extended. Insertion of a glass rod into the vagina caused a marked hyperpnoea characterized by intermittent prolonged exhalation, crouching on the fore quarters, together with extension and treading movement of the hind legs. A *second* transection of the brain stem was then made from the same level dorsally to a point just rostral to the mammillary bodies. Stimulation of the external genitalia and insertion of a glass rod into the vagina were followed by reactions identical to, but weaker and less easily elicited than, those described in the preceding paragraph. A *third* transection was made through the brain stem at the intercollicular level, and was followed by the development of good decerebrate rigidity. Stimulation of the genitalia, both manually and by glass rod inserted *per vaginam*, was followed by no reactions comparable to those described above.

Mesencephalic lesions

Complete transections. Completely negative results, similar to those described in the preceding paragraphs, were obtained in several experiments in which the mesencephalon was totally transected at the intercollicular level. Seven guinea pigs were injected with oestrin, and progesterone was administered 48 hours later. Immediately following the injection of progesterone, 4 animals were decerebrated at the intercollicular level by the Sherrington trephine method and 3 by the anemic method developed for the cat by Pollock and Davis (1924). Likewise, similar transections were produced in 3 oestrous cats. In all cases marked decerebrate rigidity developed immediately after the operation, but in no case was any response obtained which even remotely resembled oestrous behavior.

Partial transections. Experiments were next undertaken which were designed to test the assumption that the failure of the decerebrate animals to show oestrous responses was due to specific interference with the reflex mechanisms by means of which these responses are mediated rather than to general systemic effects. The mesencephalon was partially transected by means of the sucker. The cut extended completely across both inferior colliculi to depths varying from the dorsal margin of the central gray around the aqueduct of Sylvius (Fig. 12, 13 and 14) to the aqueduct itself. These lesions were well tolerated by the 3 guinea pigs in which they were produced. Repeated injections of oestrin and progesterone were made weekly in these animals for a period of 3 months, but in no instance was oestrous behavior observed. In addition to the loss of oestrous responses, all three of these guinea pigs showed a sensory tactile deficiency. Stimulation of the animal by touching or rubbing the hair on the back or flanks was followed by no evading reaction whatever, although normal guinea pigs react promptly to such stimulation by jumping and running away. This deficiency would seem to be confined solely to the exteroceptors in the hair follicles, since the stronger stimulation of rubbing the skin of the animals was followed promptly by evading responses. Likewise, the reactions to nociceptive stimulation, *e.g.*, pinching the skin or pulling the hair, appeared to be normal.



FIGS. 6–17. *(For legends see opposite page.)*

Lesions similar to those mentioned above, but involving the inferior colliculus on only one side, have been produced in 4 animals. These individuals also show a tactile deficiency which is sharply limited to the side of the body opposite the lesion. Likewise, exactly similar symptoms were observed in 2 animals in which one superior colliculus was destroyed in the same fashion. Injections of oestrin and progesterone have been made repeatedly into these animals and in two instances oestrous responses were obtained. These responses, however, were weak and required such strong stimulation that the laterality of the reflexogenous zone was not determinable.

Spinal cord lesions

Complete transections. Transections of the spinal cord at levels ranging from L2 to T5 were made in a series of 8 spayed guinea pigs. After recovery from the operation the spinal reflexes were tested repeatedly, both before and after the injection of oestrin and progesterone. No change could be found in the spinal reflexes which was correlated with the endocrine condition of the animal, and in no case was any reflex obtained which was at all suggestive of the responses which normally are obtained at oestrus. Three animals, however, were observed to utter a purring vocalization which frequently accompanies oestrus when the skin and hair on the back were stimulated above the level of the transection.

Hemisections. In 3 spayed animals an attempt was made to hemisect the spinal cord laterally at the C2 level. After recovery from the operation, these animals were injected with oestrin and progesterone and tested for sexual behavior. Completely normal responses were obtained repeatedly from all three; the reflexes involving the hind-legs and perineum were bilaterally expressed. These responses, however, could be obtained only by stimulating the hair on the side opposite the lesion, while stimulation of the side ipsilateral to the lesion evoked no response whatever. These animals were also tested for the tactile deficiency mentioned above during the intervals between the

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FIG. 6, 7 and 8. Transverse sections through the optic chiasm, mammillary bodies and posterior commissure of the decorticate guinea pig shown in Fig. 1 and 2. Thionin. ×7.

FIG. 9, 10 and 11. Transverse sections through the region of the optic chiasm of the brain of a guinea pig in which the septal regions had been removed and the pre-optic area injured. Normal oestrous responses were obtained from this animal. Thionin. ×7.

FIG. 12, 13 and 14. Transverse sections through the region of the inferior colliculus of the brain of a guinea pig in which the mesencephalic tectum was partially transected at the level of the inferior colliculi. No oestrous responses were obtained from this animal, and a sensory tactile deficiency was also present (see text). Thionin. ×7.

FIG. 15. Transverse section through the C2 segment of the spinal cord of a guinea pig after hemisection. Bilaterally expressed oestrous responses were obtained, but only after stimulation of the normal side. Hematoxylin and eosin. ×8.

FIG. 16. Transverse section through the C2 segment of the spinal cord of a guinea pig after destruction of the posterior quadrant. The behavior of the animal was identical with that of the animal shown in Fig. 15. Hematoxylin and eosin. ×8.

FIG. 17. Transverse section through the C2 segment of the spinal cord of a guinea pig after destruction of the anterior quadrant. The oestrous behavior of this animal was completely normal. Hematoxylin and eosin. ×8.

oestrous periods induced by the hormone injections. All three individuals showed the deficiency on the side ipsilateral to the lesion, while normal evading responses were obtained from stimulation of the hair on the contralateral side.

Histological examination of sections from the C2 segment showed that complete hemisection had been produced in only one of the three cases. The lesion was practically confined to the posterior quadrant in one case, while in the third case considerable damage was done to the anterior quadrant in addition to complete destruction of the posterior quadrant (Fig. 15).

Posterior quadrant section. The posterior quadrant of the cord was sectioned at the C2 level in 2 animals. After the operation, both failed to show evading responses when the hair was touched on the ipsilateral side, while stimulation on the side contralateral to the lesion was followed by these reactions. One animal failed to make a good recovery from the operation and died a few days later, but injection of the remaining animal with oestrin and progesterone was followed by oestrous responses which were bilaterally expressed but which could be elicited only by stimulating the side contralateral to the lesion. Examination of the C2 segment of the cord showed that the lesion had successfully interrupted the posterior column, Lissaur's tract and other regions in the posterior quadrant (Fig. 16).

Anterior quadrant section. Lesions involving one anterior quadrant of the cord also were made at the C2 level in 2 animals (Fig. 17). After recovery, evading responses were obtained from either side of the animals, and, after injection with oestrin and progesterone, completely normal bilaterally expressed oestrous responses could be obtained from stimulation of either side of the animal.

Discussion

The experiments just described constitute proof that normal sexual responses can occur in the complete absence of the neocortex and of certain other portions of the forebrain in the guinea pig. Likewise, it has been shown elsewhere that there is in the electro-encephalogram of guinea pigs no change which can be correlated with the state of sexual receptivity (Dempsey, unpublished data). These experiments are in complete agreement with those of Bard and Rioch (1937), Bard (1936), and Brooks (1937), and show that normal oestrous responses can occur in animals which have been deprived of neocortex.

In addition, it has been demonstrated that lesions involving the septal regions and other medially located structures do not interfere with the oestrous responses. Likewise, oestrous responses have been obtained in acute experiments after removal of all tissue in front of a plane extending from the anterior limits of the superior colliculi to the anterior margin of the mammillary bodies. However, removal of the mammillary bodies by a second transection of the brain stem and transections at the intercollicular level abolish the oestrous responses. These experiments indicate that a fundamental part of the mechanism which controls the mating reactions is located caudal to the

anterior margin of the mammillary bodies and rostral to the intercollicular level. The loss of the sexual reactions after destruction of the colliculi can best be interpreted as due to an interruption of the afferent pathways associated with these responses (see below). This constitutes further evidence that the caudal limit of the region which controls the mating responses lies at a level anterior to the colliculi.

A normal female guinea pig, when not in heat, shows evading reactions to the same stimulus which evokes sexual behavior when the animal is in heat. Both the evading reactions and the sexual responses are lost with the same lesions of the colliculi and of the cord, whereas both are bilaterally preserved in surviving hemidecorticate animals and animals with asymmetrical septal lesions. It therefore seems likely that the same exteroceptors and central ascending pathways are involved in both of these patterns of behavior. The fact that unilateral lesions of the colliculi abolish the evading reactions from the contralateral side, but cause a general depression of the oestrous behavior, does not necessarily constitute evidence against the above hypothesis, but may only indicate the greater vulnerability of the oestrous mechanism.

The unilateral lesions in the spinal cord and mesencephalon which have been described in preceding sections permit an approximate localization of the tracts involved in the mediation of sexual responses in the guinea pig. Since unilateral destruction of the cord or of the posterior quadrant reduces the reflexogenous zone to the side of the body contralateral to the lesion, it would seem likely that the afferent supply of the reflex responses is associated with the posterior columns and remains uncrossed in the cord. Likewise, since there is a contralateral deficiency involving the exteroceptors which set off the evading reactions and the oestrous responses after destruction of one inferior or superior colliculus, it would seem that this tract decussates somewhere below the level of the colliculi and that it runs through the tectum mesencephali. Less is known of the efferent side of the reflexes. However, since unilateral section of the cord is followed by bilaterally expressed reflexes, the efferent supply of these reflexes must cross in the cord at levels caudal to C2.

In conclusion it may be pointed out that the present experiments offer further circumstantial evidence in favor of the concept that oestrous behavior results from the action of the sex hormones on the central nervous system, and that the site of this action lies in the brain (Sherrington, 1906). Absence of changes in the electro-encephalogram and in the spinal cord reflexes, together with the evidence that long afferent paths which decussate in the hind brain are involved, suggests that the site of action of the hormones concerned (oestrin, progesterone) is on the center which has been here localized at a level between the anterior margin of the mammillary bodies and the intercollicular plane.

Conclusions

Typical oestrous responses have been obtained from ovariectomized guinea pigs after suitable hormone injections following removal of neocortex, caudate-putamen, hippocampus, septal nuclei and other portions of the forebrain.

Likewise, oestrous responses have been observed in the guinea pig and the cat after transection of the brain stem at a level just anterior to the mammillary bodies. Partial or complete transection of the brain stem at the level of the inferior colliculi abolishes sexual behavior, and it is therefore thought that the anterior limit of the neural mechanism which controls sexual behavior lies between the intercollicular level and the anterior limit of the mammillary bodies.

Unilateral lesions in the posterior quadrant of the cord are followed by completely normal and bilaterally equal sexual responses, but these responses can be evoked only by stimulation of the animal on the side contralateral to the lesions. These animals also show a tactile deficiency involving the exteroceptors in the hair follicles which is limited to the side of the animal ipsilateral to the lesion. A similar deficiency on the contralateral side is noted after unilateral lesions in the tectum. These experiments indicate that an afferent pathway for the sexual responses runs through the cord within the posterior quadrant, decussates at some point below the inferior colliculi, and runs through the roof of the mesencephalon.

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RESPONSES FOLLOWING ELECTRICAL STIMULATION OF THE CEREBELLAR CORTEX IN THE NORMAL CAT*

SAM L. CLARK
Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee

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Introduction

In 1903 Lewandowsky described, incidental to some experiments of a different type, a method developed by Ewald (1898) for stimulating the cerebellum in conscious animals. In the skulls of 5 dogs he placed an ivory button containing two exteriorized wires which made contact with the cerebellum. The dogs were allowed to live a few days and were stimulated while unrestrained and unanaesthetized. Though his results from stimulation were inadequate, Lewandowsky observed a response during stimulation similar to that we have observed from the paramedian lobe, and from his description it is probable that this was the area stimulated in each of his 5 experiments. It is regrettable that this method lay so long unused, for it was apparently unnoticed by subsequent investigators, and it was not until the present experiments were completed that either the work of Ewald or Lewandowsky came to our attention.

Much has been learned by physiological and comparative anatomical studies of the connections and functions of the cerebellum (Larsell, 1937; Fulton and Dow, 1937). From the standpoint of the present report the most significant early work on stimulation was done by Ferrier whose book (1886) contains an excellent account of the work on the cerebellum up to that time. More recently cerebellar stimulation has been carried out largely on decerebrated animals and has been shown by several investigators to cause an inhibition of the antigravity muscles (Denny-Brown, Eccles, Liddell, 1929). Occasionally experimenters have stimulated the cerebellum in intact animals, but only a few after eliminating anaesthesia. Magoun, Hare and Ranson (1935) faradized the cerebellum of the intact monkey with the stereotaxic instrument, but under anaesthesia. The same workers later (1935, 1937) stimulated both normal and decerebrate cats and monkeys either under anaesthesia, or after recent anaesthetization. Mussen (1927 to 1934) reports experiments in which the cerebellum was stimulated in anaesthetized and a few unanaesthetized animals, employing with the latter a method similar to the one we have used. Brogden and Gantt (1937) also stimulated the cerebellum in normal, unanaesthetized dogs with an implanted electrode fed by a subcutaneous coil, after the method described by Loucks (1933) and developed further by Chaffee and Light (1934). They were not primarily inter-

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ested in exploring the cerebellum but in the study of "conditioning" to cerebellar stimulation.

None of the workers mentioned has observed completely the phenomena to be reported in this paper, but each has made observations which fit into the general scheme. From our experience in stimulating the cerebral cortex (Ward and Clark, 1936), it appears probable that the discrepancies between the various reports are mainly dependent upon two factors, *viz:* the influence of an anaesthetic, and the control of the stimulating current. While some investigators have eliminated the anaesthetic, the physical character of the currents used for stimulation has had little attention.

METHOD

Electrodes were fastened permanently into the skull of a series of cats (Nembutal anasthesia); in each case the electrode was fixed over some previously determined point on the brain. The electrode consisted of a stainless steel tube with a tapering threaded end, containing in its axis an insulated silver wire. The wire was fused into the middle of a glass rod and this encased in a rubber tube, all of which fitted tightly in the steel tube. The slightly exposed tip of the silver wire embedded in the glass rod was ground smooth, so that it could not injure the brain. The tube was screwed into a trephine hole far enough into the skull to reach the surface of the cerebellum. The end of the silver wire which was in contact with the brain through a hole in the dura mater, was the stigmatic electrode, the steel tube serving as the indifferent electrode. By means of a detachable extension cord, controlled stimuli were applied to the brain through the outer end of the electrode, which projected through a hole in the skin. The voltage of the stimulating current was controlled through a voltmeter and the length of the stimulus was determined by a timing device. In these experiments a 60-cycle sine wave current, obtained from the lighting circuit by passing it through a transformer and a variable rheostat, was used consistently as the stimulating current. The cats were unrestrained throughout the experiment. Since the effect produced from a stimulus of 4 sec. may last as long as 10 or 15 min. it is obvious that stimuli must be properly spaced if the true effect of isolated stimuli were to be observed. Not all stimuli produce visible effects of such duration, but if a long effect appeared it usually began within 90 sec. after the stimulus. In these experiments, therefore, it was the custom to allow 2 minutes or more between successive stimuli.

Three people conducted the experiments as a rule. One adjusted the apparatus and checked the time at which different events occurred, one watched the cat and dictated a detailed description of each effect as it occurred, and a third took down in shorthand the description and recorded the strength and duration of the stimulus and the times at which the changes in the cat's movements occurred. Moving pictures were made of the cats during some of the experiments for recording and for checking the dictated descriptions. In this series 78 cats were used on which a total of 94 electrodes were planted (Fig. 1).

Unless something occurred to loosen the plug in the bone, the animals survived for days or weeks and could be stimulated at will. There was no appreciable reaction about the point which touched the brain; in fact, it was usually necessary when the animal was killed to unscrew the electrode and insert a bristle at this location into the brain before removing the bone so that the point of stimulation could be found. When removed, the brains were preserved in formalin and the location of the electrode recorded. References made to the "mid-line" of the vermis refer to an S-shaped line following the highest point of the ridge which the vermis forms, and not to a mid-sagittal plane. The extent of flexures of the vermis varied from animal to animal.

RESULTS

Stimulation of the cerebellar cortex through implanted electrodes in the unanaesthetized, unrestrained cat, results in movements which vary with the position of the electrode on the cerebellum, with the strength and duration of the stimulating current, and with the immediately previous experience of the

animal. There are, no doubt, other variables as, for example, the type of stimulating current, the residual effects of anaesthesia, the effect of pre-existing posture, etc. Under reasonably constant conditions the type of response from a particular cerebellar area is constant from day to day in the same cat, and the response is similar in different cats when corresponding areas are stimulated. The typical response obtained in these experiments from cerebellar stimulation can be divided into three phases for convenience of descrip-

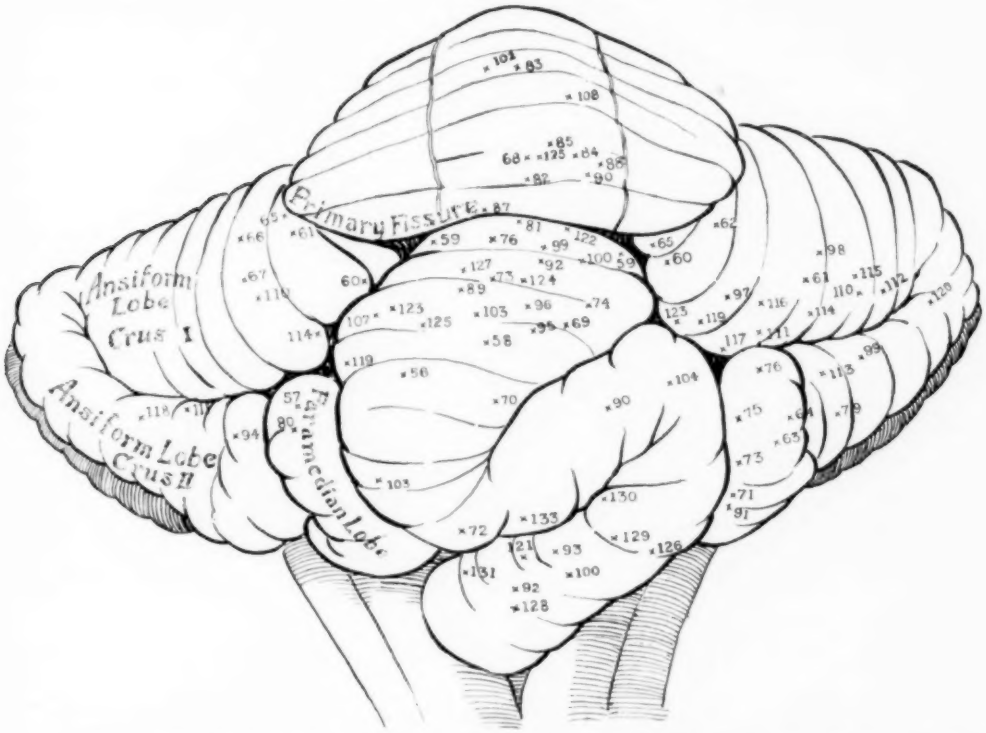

FIG. 1. Diagram of a cat's cerebellum from the dorsal surface. The serial numbers of the cats used appear adjacent to a small x which indicates the location of the point stimulated. The S-shaped vermis varies in the extent of its flexures in different animals so that the location of some points on the diagram is only relative.

tion. There is first the phase of the response which is coincident with the stimulus and brief in duration. Immediately following is the second phase, ordinarily beginning on cessation of the stimulus, usually longer in duration than the first phase, more rapid in the onset and, in terms of movement, opposite in direction. Then the third phase, which may appear as a slow continuous transformation from the second phase, or may begin after a pause of as much as a minute or more. This phase progressively involves the head, limbs, body and tail of the animal in a series of slow movements lasting for several minutes. In this paper these three phases are referred to respectively as the phase of stimulus, the rebound, and the long after-effect.

The movements produced in these experiments differ in character from the clonic portions of epileptic attacks resulting from cerebral stimulation since they are in the main tonic and slow, resembling the movements in 'slow motion' pictures. The animal actually assumes a series of statuesque postures each of which builds up gradually to a maximum, and then fades as it is replaced by the succeeding pose according to a sequence which is definite for each area stimulated. The duration of the long after-effect, and the extent

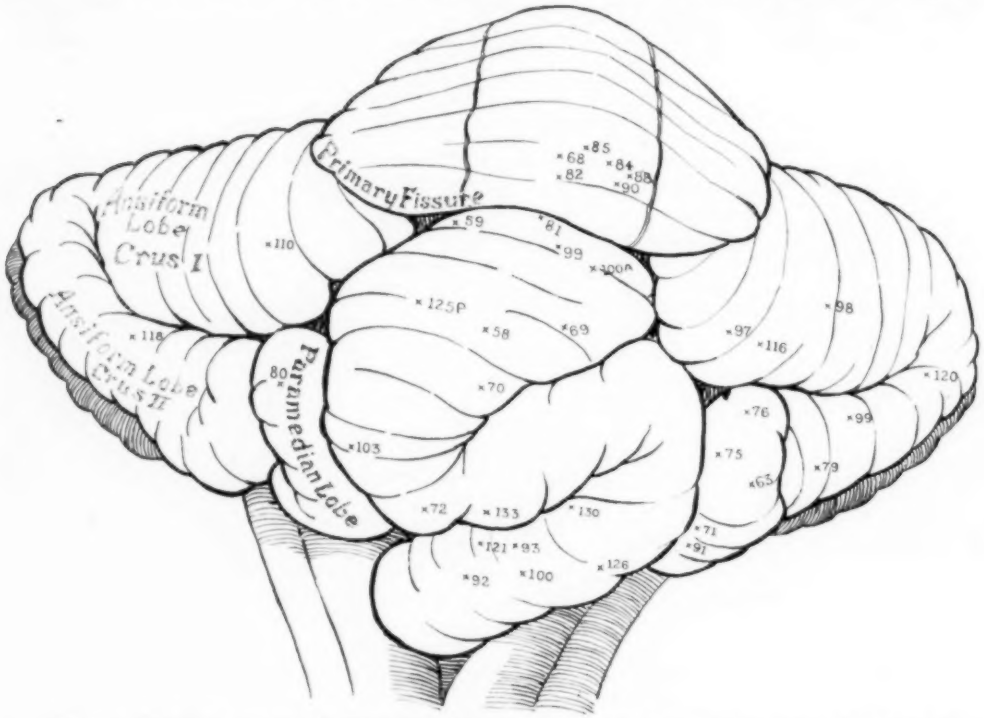

FIG. 2. Diagram of cerebellum showing the location of points on cats specifically referred to in the text as examples. The other points, omitted for the sake of simplicity conformed to the general scheme in their responses.

of involvement of the animal's parts, as well as the temporal relation of involvement of different parts, can be varied with the strength of the stimulus. A discussion of the variations in results from different strengths of stimulus can best be discussed after a typical experiment is described.

When a point on the margin of the vermis just back of the primary fissure (Fig. 2, 3, and 4) is stimulated with an adequate stimulus (2 to 5 volts for 4 sec.) the cat exhibits a series of movements lasting from 5 to 15 min. (average about 8 min.). With the stimulus the head turns gradually to the homolateral side, being held in this position for the duration of the stimulus. Promptly at the end of the stimulus the head turns toward the contralateral side in rebound. At the same time or within a few seconds afterward the homolateral forelimb may lift and protract; and may deviate in the direction of the head (Fig. 3). The foot may wave slowly and even be lifted higher than the head.

After about half a minute or a minute the animal returns to its normal resting posture or may go directly into the long after-effect. If the homolateral limb did not lift at first it now goes through the procedure. At this time the head may or may not turn tonically to the homolateral side. The forelimb gradually relaxes, while the contralateral forelimb becomes involved in a similar manner, and the head may turn to the contralateral side. By $2\frac{1}{2}$ to 3 min. after the stimulus these movements have subsided. There may appear a concavity of the trunk to one side then the other along with or following the forelimb involvement. About 4 to 5 min. after the stimulus the homolateral hindlimb

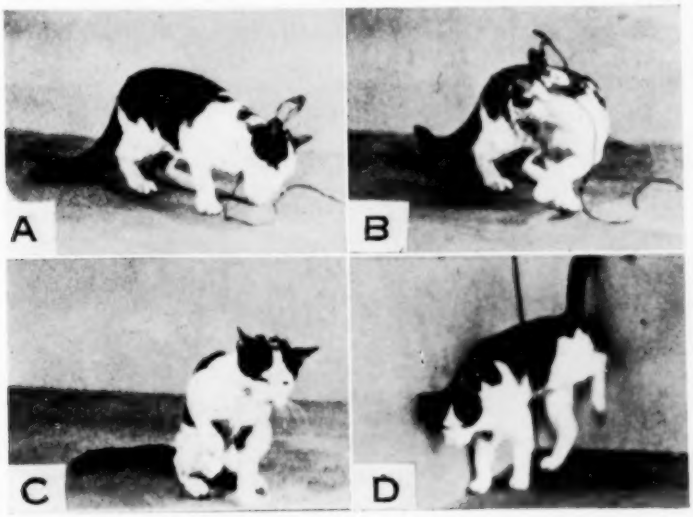

FIG. 3. A to F (Fig. 3 and 4). A series of frames from a moving picture taken of cat 125 following a stimulus of 4 volts for 4 sec. to a point on the left side of the vermis 3 folia back of the primary fissure. A, during the stimulus, the head slightly to left. B, about 3 sec. after the stimulus, the head of the cat is to the right in rebound and the left forefoot is being held up. C, 3.75 min. after the stimulus, the right forepaw being held up. D, 7 min. after the stimulus the left hindlimb is being lifted and retracted.

begins to be affected, and lifts as did the foreleg showing an overaction of different groups of muscles in the extremity, so that its position gradually changes. It may be protracted awhile, then retracted, and the hocks may deviate medially then laterally. The tail at this time tends to curve tonically toward the homolateral side so that it is in a horizontal plane with tip pointing toward the head. These effects gradually give way and at about 6 or 7 min. after the stimulus the contralateral hindleg shows an effect like the homolateral (Fig. 4); the tail hooks to the contralateral side, sometimes showing a stage where it hooks dorsalward and at other times resembling a corkscrew in the period of transition from one side to the other. As these effects gradually cease the animal returns to normal.

In between the phases of such an attack there may be short intervals in which the animal stands or sits quietly or exhibits some voluntary or reflex activity such as eating or scratching or licking itself. There is, however, an obvious quieting of the animal until the effect of the stimulus is over, and the animal often appears as if preoccupied. In between the periods of marked limb involvement the cat may turn in small circles in the direction indicated by the head turning or concavity of the body. If the animal walks or jumps

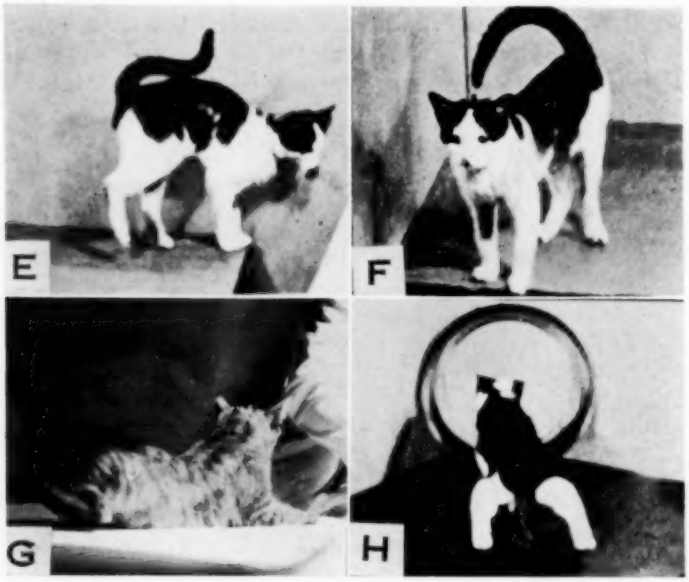

FIG. 4. E. 8.5 min. after the stimulus the right hindlimb is being held up and the tail is curved over the back. F. 8 min. and 50 sec. after the stimulus, the hocks are still turned in and the tail is curved to the right. Later the tail turned left and the cat lay down on its right side. G. Cat 60, showing lifting of right hindleg with cat still lying prone, as part of the after effect of a stimulus to an electrode on the right side of the cerebellum. H. Cat 98, 3.5 min. after stimulation showing the way the hocks turn outward.

while the limbs are involved, an obvious dysmetria is manifest in the movements of the affected extremities.

Such is the typical history of a long effect when the point on the vermis is not in the midline. This is the type of experiment described in a preliminary report (Clark, 1937). It appeared likely from these results that a stimulus applied to a point in the midline might involve the animal in an attack in which the limbs of both sides would be simultaneously affected. This was found to be true, though due to the difficulty of planting a point exactly in the median plane, there is usually a slight lead of one or the other extremity, or a turning of the head to one side then the other. Following is a protocol from such an experiment:

On September 13 a plug was planted near the midline in cat 81, the point

proving on subsequent examination to be just on the posterior margin of the primary fissure, slightly to the left of the midline (Fig. 2). On September 15, after some preliminary stimulations of less intensity, a stimulus of 5 volts for 4 sec. produced the following: slight retraction of the head; when the stimulus ceased, there was a sudden rebound as the cat's head tucked down beneath its chest, the top of the head nearly touching the floor. This gradually subsided and the cat then slowly stood higher in its fore quarters. At 1 min. 20 sec. after the stimulus the left foreleg was lifted in high flexion. At 1. min. 35 sec. the right leg lifted once, the head turned to the right, and at 1 min. 45 sec. both forelegs were lifted from the floor and the cat sat on its haunches. This posture was maintained for about 20 sec. and first one then the other foreleg was placed on the floor. As one foot was put down the other was lifted. This continued until 2 min. 35 sec. after the stimulus. At 3 min. after, the cat walked cautiously forward with evidence of overstepping in the hindlegs, especially the left, which was lifted too high with each step. At 4 min. 20 sec. the cat lifted its right hindleg in high flexion, and walked, hopping on its left hindleg. This continued until 5 min. 40 sec. after the stimulus when the right leg was lowered. At 6 min. after the stimulus the cat stood with feet bunched in a small area. The hocks were turned in, the tail turned to the left, and the hind quarters crouched low. At 6 min. 30 sec. the tail turned to the right and the hocks touched in walking. At 7 min. 30 sec. after the end of the stimulus the tail turned to the left, and then the cat quickly returned to normal.

The patterns of response in such a long effect vary with the region of the cerebellum. The head movements are especially interesting when the point is near the midline. When the point is just rostral to the primary fissure (cats 68, 82, 84, 85, 88, 90, Fig. 2) during the stimulus the head goes down toward the floor (and sometimes forward), and in the rebound rises high (and sometimes backward) in the opposite direction, with perhaps deviation to one side and then the other as well. Back of the primary fissure (cats 58, 59, 81, 99, 100A, 103, 72) the effects of stimulation are just the reverse: during the phase of stimulus the head rises high, and in rebound the head is carried down. With the movements up and down may be combined horizontal movements of the head so that the head moves up and backward with the stimulus, down and forward in rebound, and perhaps deviates first to one side and then the other.

When the point is on the paramedian lobe (cats 63, 71, 75, 76, 80) on stimulation the animal leans to the opposite side and simultaneously lifts the homolateral forepaw. At the end of the stimulus there is no marked rebound, the animal merely returning to its original position; thus far we have been unable to obtain evidence of a prolonged after-effect with lifting of all extremities from any of the points planted on this area. The homolateral forelimb may show some effect, *e.g.*, overstepping and disturbance of the placing reactions for a minute or more. There is a tendency for the cat to cringe when the paramedian lobe is stimulated. This is the only region giving much evidence of disagreeable reaction; the cats frequently purr throughout an experiment.

The results of stimulation of points near the vermis on Crus I of the ansiform are similar to the effects obtained from the vermis. Further away from the vermis, as in cats 97, 98 and 120, though the effects upon the forelimbs were separated in point of time of involvement during the long after-effect, the hindlimbs tended to become involved simultaneously. However, in cat 116, in which a plug was planted on the right ansiform (Crus I) on June 27, a stimulus on June 30 gave the following sequence in the long after-effect; the right foreleg was involved for 2 min., then 20 sec. later the left foreleg became involved, and was affected for about 1 min.; then at 4 min. after the stimulus the *left* hindleg began lifting and showed evidence of involvement for more than 2 min., overlapping the effect on the right hindleg which began to be involved at 5 min. after the stimulus. There was, therefore, a reversal of order in the effect on the hindlimbs as compared with the sequence obtained from points on the vermis, and this was observed on three different occasions. A similar reversal appeared once in cat 97, whose point of stimulation was in the same region as that of 116, and once in cat 70, whose point was on the right margin of the vermis considerably medial to that of the other two cats. This response from cat 70 was of further interest since the long after-effect was delayed in beginning, the right foreleg not lifting until 3 min. 30 sec. after the stimulus.

The effects from Crus II differed somewhat from those obtained from Crus I of the ansiform lobe. Points on the medial portion of Crus II produced effects similar to those on the nearby paramedian. Further laterally, as in cats 118 and 99, the long after-effect appeared, with the forelimbs being affected in the usual sequence (homolateral, then contralateral) but with the hindlimbs being involved practically at the same time, as in Crus I. It was in the ansiform lobe that effects on the eye and ear were observed. In cat 118, for example, with the stimulus the homolateral eye closed and the homolateral ear flattened, the opposite ones were similarly affected about 4 min. after the stimulus.

The effects obtained from points on the most posterior exposed portion of the vermis (92, 93, 100, 121, 126, 133) gave evidence of another variation in the general scheme. With gentle stimulation, if the point was not in the midline, the cat leaned toward the side stimulated uncovering the opposite hindlimb if seated, and it might abduct and extend the opposite hindlimb as if to prop the body. As the stimulus ceased the rebound occurred and is the mirrored image of the first effect. That is, the cat leaned toward the opposite side, withdrew the extended hindleg and placed the homolateral one in the propping position. With a weak stimulus, the seated cat might, as it leaned with the stimulus, make one hopping adjustment of the homolateral foreleg to support it in the leaning position. The leg returned to a natural position at the end of the stimulus.

These movements have the appearance of normal adjustments of the body to changes in the tension of groups of muscles, and, indeed, their counterpart can be produced by placing the hand on one side of a standing cat in the region of the thigh (or even of the shoulders) and pushing gently towards the opposite side. The cat leans against the pushing hand and abducts the

contralateral hindlimb as a prop to keep from being pushed over. If a quick change is made and the cat pushed from the other direction, it changes its position as it does in rebound to a stimulus. If a weak stimulus in this region actually produces a response from the cat comparable to that obtained by pushing the cat's body gently towards the contralateral side, then the effects of a stronger stimulus would not be unexpected, for a stronger stimulus caused its hind quarters to tend to fall (or actually fall) toward the contralateral side, and rebound at the end of the stimulus toward the homolateral side. In the case of the stronger stimulus the cat appears unable to adjust to the new situation until it has fallen in the direction indicated—just as with a stronger push it falls before it can adjust itself.

When the stimulus in this posterior part was in the midline, the cat did not fall in either direction but sank to the floor and extended its claws as if holding on. At the end of the stimulus it might rise again or lean towards one side. As yet we have not obtained much evidence of a long after-effect from the more posterior region of the vermis, though from cat 100 an effect of 1 min. 45 sec. involving tail and body occurred, but there was not the high lifting of limbs. From a point slightly anterior to this on cat 130 a long after-effect of about 8 min. duration occurred, involving all limbs and tail in the usual sequence.

Certain phenomena common to the long after-effects are obvious as one watches those obtained from various places on the cerebellum. First, there is the slow character of the movements elicited, common to all parts involved. The change from stimulus phase to that of rebound is usually rapid, but there follows a posture which is tonic and subsequent changes are slow. Furthermore, while the pattern in which portions are involved differs somewhat with the point stimulated and while the stimulus and rebound phases may differ in direction and character, movements of specific parts obtained from stimulation of various areas of the cerebellum have certain common qualities.

In the case of limb movements, for example, there is usually evidence that an extremity is becoming involved by the extension of the claws or extension and retraction of claws as in the kneading movements of cats (the 'pleasure reaction'). Then there is a tenseness in the extremity and a slow lifting. The lifting is interrupted for awhile by alternate periods of relaxation and the foot returns to the floor only to lift again until it is held at its highest point. There is a corresponding adjustment of the other parts to balance the animal. The position of the forelimb in its extreme state of lifting varies with the animal (apparently dependent on the point stimulated and the strength of the stimulus). It may be over the head, or extended in front of the animal or held flexed close to the chest wall. Often the lifted foot waves slowly for awhile. As the foot is returned to the floor it reverses the effect seen in the beginning. That is, the foot is dropped slowly and then lifted again, dropping more with each movement, but when it reaches the floor it may be lifted quickly again and again as if the floor were too hot to rest upon. There is at times evidence of hypersensitivity to touch in the involved extremity, and it will withdraw

suddenly on being stroked. When two extremities are involved nearly simultaneously each shows the same effect, and the one first involved may lift, only to be suddenly replaced on the floor for the opposite one to lift. As mentioned above it is possible for the cat to lift both forefeet at once (*e.g.*, 58, 68, 69, 120) and sit on its haunches for half a minute more or less. When this occurs, the extremity which first showed the effect also loses it first; and the cat will tentatively replace that foot on the floor leaving the other one lifted until the effect dies out in it.

Not only is lifting a characteristic of the limb movement, there are abduction and adduction, protraction and retraction, internal and external rotation, especially noticeable in the hindlimbs as the cat walks during a response. Frequently the hindlimbs were raised too high with each step and kickback before the foot descended, so that it landed almost in the place from which it was lifted and little progress was made. When both hindlimbs were involved the gait of the animal was strikingly like that which we observed (Ward and Clark, 1938) in a few animals following the clonic phase of epileptic seizures elicited by electrical stimulation of the cerebral cortex. Both before and after the stage of marked lifting of the limbs, the limbs involved showed dysmetria as the cat walked or jumped. One cat, jumping from the floor to a table toward the end of a long after-effect, twice jumped about six inches too high; this being the only visible evidence that the hindlimbs were still involved. Shortly after this the cat jumped to the table with its usual smoothness and accuracy.

Throughout the long after-effects it was obvious that the movements that occurred were paired in opposite phases; just as is the case with the movements of the stimulus and rebound (Fig. 5). For example, the head would turn to one side for awhile and then turn to the other; the head might be held back and high up, but shortly afterward it would go down and forward (or vice versa); the body would be concave to the one side, then to the other; the shoulders would be high, then low, the tail would be turned first to one side and then to the other, or it might hook ventralward between the cat's legs and then curved dorsalward over its back (at times of transition in attempting to turn to both sides at once the tail may resemble a corkscrew); the cat might stand high on its hind quarters and then sink low; the hocks may be turned in so that they touched as the cat walked and later be turned markedly out (Fig. 4). In some animals the ear was flattened on the homolateral side and the homolateral eye closed, while the contralateral ear and eye were not affected until later (cats 110, 118). All such movements occurred slowly, consuming from a few seconds to more than a minute just as in the case of the lifting of the limbs. And in each cat these movements occurred in a definite sequence so that having witnessed a long effect from stimulation of a certain point, one can predict with reasonable accuracy just when each movement will occur after a succeeding stimulus. Not only is the sequence the same but the time after the stimulus at which one may expect a phase of movement is approximately the same for stimulations of comparable intensity.

There was an optimum stimulus for the production of the long after-effect, and it was usually of greater strength than that necessary to produce only the phases of stimulus and rebound. As stimuli at a point were gradually increased, a threshold strength was reached at which there was only a slight effect during the stimulus and a slight rebound or, since the rebound was usually more conspicuous than the stimulus phase, there may be no visible effect during the stimulus, but the rebound nevertheless follows. Then, as

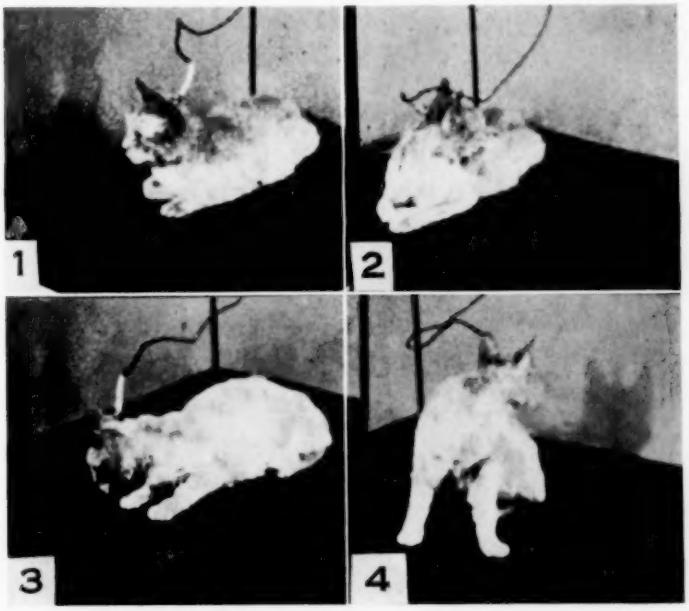

FIG. 5. Cat 95, whose point was on the right side of the vermis 3 folia back of the primary fissure. Pictures 1 and 2 show respectively the phases of stimulus and rebound following a weak stimulus. Pictures 3 and 4 show similar phases following a stronger stimulus, with obviously more marked effects. In 1 and 2 the head is turned slightly to the right, in 3 and 4 it is turned markedly to the left. The wire lead used in stimulating is shown attached to the electrode.

the stimulus was increased further, the motion in the first two phases became greater (Fig. 5). With still greater increase there might occur the phase of stimulus, followed by the phase of rebound, followed by only the first part (more or less) of the long after-effect. When the optimum strength was reached there occurred the three complete phases just described. If this optimum strength of stimulus was surpassed, the different phases might become telescoped, so that increasing the stimulus too far beyond the optimum tended actually to shorten the total duration of the visible effects.

Excessively strong stimulation not only caused a telescoping of the various effects obtained from a point, but it sometimes produced others as a by-product. For example, in cat 116 (right ansiform, Crus I) it caused the cat to fall to the right and the cat's tail rotated counter clockwise to one facing

the cat. A cat's tail will rotate in this direction if it is made to lean or fall on its right side. Too strong stimulation caused cat 85 (anterior vermis) to turn somersaults, and cat 79 (right ansiform, Crus II) to roll over two or three times towards its right. Occasionally (cat 59) after an optimum stimulus, when all parts of the animal have been involved in sequence, a new series of movements began with turning of the head and lifting of the homolateral forepaw, but as yet a second series has not continued beyond this. There has occurred, too, a repetition of the effect on the homolateral forelimb just after the effect on the contralateral forelimb (cats 60, 99 (middle), 100, 125P).

It is possible to mask or prevent the appearance of the long after-effect by stimulating at a strength that is too great, or by stimulating at intervals that are too close together, or by stimulating too recently after an anaesthetic. A long effect has not yet been obtained from an animal incompletely recovered from the anaesthetic; frequently more than 24 hours in the case of nembutal. After one or more successful stimuli it may not be possible to obtain the long after-effect until several hours have elapsed. However with cat 81, a day following implantation, three long reactions were evoked, each more than 7 min., within a half hour. And after several days of successful stimulation a point may cease to give the long after-effect though the stimulus and rebound phases persist. A rise of threshold usually accompanies such a change. Small injuries to the cerebellum in the neighborhood of the point sometimes appeared to abolish the long after-effect. In some animals, in which a technical fault occurred, a long after-effect may not be obtained from a region known to produce such effects, though the first two phases occur.

Deviation of the eyes toward the side stimulated has occurred in some cats during the stimulus, and was associated with or preceded the turning of the head in that direction. Likewise, in the phase of rebound, the eyes may deviate to the opposite side accompanying or preceding the turning of the head in that direction. Nystagmus was not uncommon following the stimulation of the cerebellum, and was observed once, with weak stimuli; it was replaced by constant deviation following stronger stimulation. The observations of eye movements and changes in the pupils have been limited by the necessity of watching other movements. We have not observed contraction of the pupils as did Ferrier, and Hare, Magoun and Ranson (1937) on stimulation of the cerebellum, though dilatation has been frequently seen. No other effects on autonomically innervated structures have been noted except that in some animals a fluffing of the tail accompanied an after-effect following a strong stimulus.

Circling has appeared in most of the long after-effects, usually just following the rebound phase, but sometimes later. The cat, having turned its head toward one side, merely walks around in that direction one or more times in a small circle. Some animals during the circling may lie down on the convex side just as a cat does normally when it curls up to rest. Other examples of such 'opportunism' appear occasionally. A cat may utilize the position of its turned head to lick the nearby shoulder, or the upraised paw may be used to

rub the back of the head (the head being free from involvement at the time and taking the initiative).

The responses evoked, while influenced to some extent by the position of the cat, may cause spontaneous activity to cease. Cat 60, for example, was stimulated while playing with a string. The play was interrupted by the artificially induced movements of the forepaws. A cat that is eating will stop while the influence is affecting the head and fore quarters but may eat normally while the hindlimbs are affected. A cat lying in a sphinx-like position will still lift a hindlimb without rising when that limb becomes involved (Fig. 4). On the other hand, when the effect is weak in an extremity spontaneous activity will mask it, or obliterate it during a voluntary movement.

Discussion

While the results described in these experiments from cerebellar stimulation are not identical with those of any previous investigator, many of the stages of special movements which are reported here resemble markedly portions of experiments described by others. For example, our observations of deviation of head and eyes agree in general with those of Ferrier and of Bechterew (as cited by Tilney and Riley). Horsley (1906) has reported that he and Clarke were unable to elicit movements from stimulating the cerebellar cortex but the movements from stimulation of the central nuclei are not unlike some we have obtained from the cortex. They observed deviation of the head and eyes to the same side from one area, and powerful bicipital flexion of the elbow from another, etc. They report the eye movements as steady with no clonic intermission and no after-effect when the stimulus ceased. The familiar effect of stimulating the cut surface of the mesencephalon as described by Graham Brown (1913, 1915) has much in common with certain stages in the movement from stimulation of the cerebellar cortex: homolateral bending of head and tail, flexion of the homolateral forelimb, etc. It is significant that Graham Brown observed that the posture was often maintained after the stimulus ceased; the ipsilateral flexion (or contralateral extension) outliving the evoking stimulus several minutes. And he found that stimulating the contralateral red nucleus during the phase of after-discharge produced a rebound phenomenon.

Denny-Brown, Eccles, and Liddell (1929) in addition to inhibition of the antigravity muscles in decerebrate rigidity, observed that in animals in which the level of decerebration is high, cerebellar stimulation may elicit "sharp flexion of the elbow joint, flexion (dorsi-flexion) of the wrist, abduction and extension of the digits and protrusion of the claws." They describe the position of the forelimb as resembling that of the 'rampant' animals of heraldry. Further, they observed that "after and sometimes during the stimulation the limb 'strikes' by the elbow becoming extended, the wrist and fingers flexed." Mussen has described specific responses from small areas of the cerebellar cortex. While we have not confirmed the details of these experiments, many

of the movements he describes we have observed in the course of long after-effects.

The descriptions of the effects of cerebellar stimulation with the stereotactic instrument on intact and decerebrate monkeys and cats given by Hare, Magoun, and Ranson (1937) contain points of extreme interest in application to the present experiments. They have observed movements in two phases (an inhibition of a posture or the assumption of a new position) during the stimulus, and a second phase following the stimulus, usually contrary to the first, appearing as a rebound. While they did not obtain the successive movements we have seen in the long after-effects, they observed the long duration (in some instances 5 minutes) of the effect of a stimulus. In addition to movements involving the trunk and limbs of an animal all at once, the effects on the homolateral forelimb alone are not unlike some of the movements we have obtained. There are a number of other features of their experiments which have much in common with the present report. The fact that the phase of stimulus and rebound which we have observed occur from stimulation of the cerebellar cortex is not so surprising, but in comparing the present results with certain previous reports of cerebellar stimulation, the direction of movement during the phases of stimulus and rebound from various areas is significant.

Both in the monkey and in the cat Ferrier observed that stimulation of the cerebellar vermis produced movements of the eyes. Stimulation anterior to the primary fissure caused the eyes to move upward, while stimulation back of the primary fissure caused them to move downward (with a deviation toward the homolateral side if the electrode was not in the midline). Ferrier states in connection with experiments on the monkey (1886, p. 189) "When the head is allowed free play the movements of the head coincide with movements of the eyes," and at times he observed involvement of the limbs. He pointed out that stimulation of this anterior portion of the cerebellum excites muscular combinations which would counteract a tendency to fall forward; and that stimulation of the vermis more posteriorly excites muscular combinations which would tend to prevent the animal from falling backward. "We should therefore expect to find," he continues (p. 199), "that a lesion which annihilates the functional activity of any of the individual cerebellar centers should manifest itself in a tendency to the overthrow of the balance in the direction naturally opposed by this center. This also is in accordance with the facts of experiment." That is, he found that destruction of the "anterior part of the median lobe (monticulus)" results in a tendency for the animal to fall forward; while destruction of the "posterior part of the median lobe (declive monticuli)" produces a tendency for the animal to fall backward (movements opposite in direction to those he obtained from stimulating these areas). Mussen (1931) later expressed similar ideas and reported similar results. Ferrier states that Flourens and Renzi in 1864 observed the effects of lesions on the vermis as described.

There is an apparent conflict between these statements and the observa-

tions reported here. Both Ferrier and Mussen stated that the effect of stimulating the anterior or posterior vermis was opposite, so far as the contracting muscles were concerned, to the effect of removal of the same part of the vermis. We have found, on the other hand, that the movement during the phase of stimulus of anterior or posterior vermis is similar in direction to the posture obtained on removal of the part stimulated while that in the phase of rebound is the opposite. An obvious corollary to this statement is that removal of one portion of the vermis (anterior or posterior) causes an effect similar to the rebound which follows stimulation of the opposite portion of the vermis in the intact animal. The accompanying table will illustrate this point.

Table 1. The anterior and posterior vermis compared

	Anterior vermis	Posterior vermis
Removal Flourens & Renzi Ferrier Mussen	Head held down (animal tended to fall forward, anterior neck muscles contracted)	Head held up (animal tended to fall backward, posterior neck muscles contracted)
Stimulus Ferrier Mussen	Head goes up (posterior neck muscles contracted)	Head goes down (anterior neck muscles contracted)
Present experiments	Stimulus—head down Rebound—head up	Stimulus—head up Rebound—head down

Evidently Ferrier and Mussen saw in stimulating the vermis only the phase of rebound seen in our experiments. Ferrier's statement is significant at this point (1886 p. 190), "It is also to be noted, in reference to electrical irritation of the cerebellum, that occasionally stimulation is absolutely without effect at first, and that after the lapse of some time the phenomena follow with great precision." It is possible that working with animals recently anaesthetized a stronger stimulus was necessary, and we have frequently observed that a stimulus stronger than optimum will cause the rebound phase to begin before the stimulus actually ceases; furthermore a brief but intense stimulus might give insufficient time for the appearance of the excitatory phase, but, on cessation, allow the appearance of the rebound. In the present experiments a stimulus about 4 sec. in length brought out the phases to best advantage.

The mixed representation of afferent fibers from different bodily areas in the same portion of cerebellar cortex is significant (this point is discussed by Hare, Magoun and Ranson, 1937). Since the cerebellar cortex is nearer the afferent side of the reflex arc than the efferent side, if one measures distance by the number of synapses in the neuronal chain, stimulation must have something in common with the reception by the cerebellum of a mass of afferent impulses. A presentable theory could be built up which would explain the movements elicited after electrical stimulation of the cerebellar cortex as

actual responses to an artificially induced sum of 'proprioceptive information,' the movements being identical with those that would follow from a posture that would present to the cerebellum a similar body of normal proprioceptive impulses. Much of the cerebellum remains to be explored, but we have stimulated directly some point on all but one (the vestibular flocculonodular lobe) of the four principle subdivisions into which Larsell (1937) divided the cerebellum from a functional viewpoint.

Summary

Electrical stimulation of the cerebellum in normal unrestrained cats is followed by visible movements involving the various parts of the animals' musculature. Such movements may appear in three phases; the first with the stimulus; the second appearing as a rebound opposite to the first and immediately following the end of the stimulus; the third, prolonged and involving the various parts of the animal in a series of relatively slow movements in a definite sequence lasting several minutes.

The pattern of movements which may be elicited from the same point in a cat from day to day remains the same both with respect to the character of the separate movements and the time of their appearance in the sequence. Different large areas of the cerebellum respond to stimulation with patterns of movement having a recognizable specificity for the area. There is a certain common quality to the movements elicited from the cerebellum which is different from the movements that occur in clonic phases of epileptic attacks provoked by stimulating the cerebral cortex.

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SIMULTANEOUS ELECTROMYOGRAMS AND ELECTRO-ENCEPHALOGRAMS IN PARALYSIS AGITANS*

ROBERT S. SCHWAB AND STANLEY COBB

From the Departments of Neurology and Psychiatry, Massachusetts General Hospital, and the Departments of Neurology and Neuropathology, Harvard Medical School, Boston

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IN AN EFFORT to discover the origin of the rhythmic tremor characteristic of post-encephalitic and arteriosclerotic paralysis agitans, simultaneous elec-

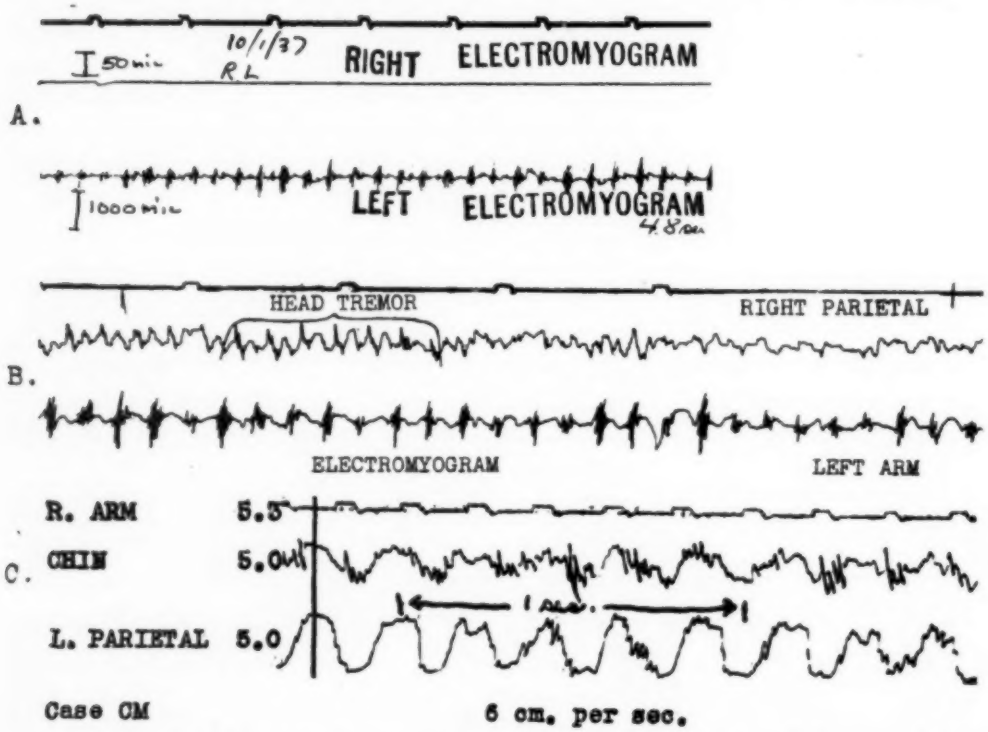

FIG. 1 A. Simultaneous electromyograms in right and left flexor digitorum sublimis in patient R. L., with left-sided paralysis agitans. Note there is no electrical activity in right arm which is a base line, free of artifacts with this degree of amplification from surface electrodes.

B. Simultaneous electromyogram and electroencephalogram in patient with severe bilateral paralysis agitans. The spikes that appear in the head lead as synchronous with the arm tremor are artifacts due to movement of the head electrodes.

C. Simultaneous electromyograms from chin, and arm (recorded through timing pen), and electroencephalogram, showing synchronous waves.

tromyograms and electroencephalograms were recorded from 37 patients. If the tremor originates from a rhythmic discharge in the brain, strong enough

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in some cases to involve all extremities and dominate the motor activity of the individual, one might hope to be able to record it from electrodes placed on the intact skull. Discharges as slow as 4 to 6 per sec. might be expected to build up enough potential to be picked up, even if the seat of the disturbance is well beneath the outer cortical layers. The patients were selected from the Neurological Service of the Massachusetts General Hospital (Service of Dr. J. B. Ayer) and a few private patients of the authors. Fifteen of the 37 were classified as post-encephalitic and 22 arteriosclerotic, but the classification is not accurate as it was often impossible to get a history of encephalitis in the

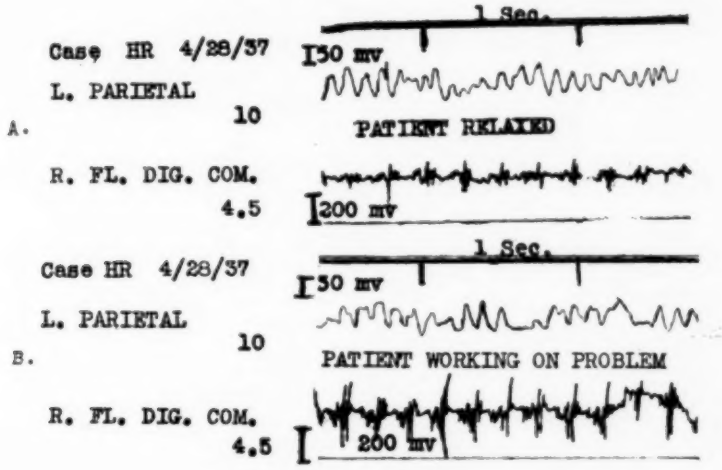

FIG. 2. Simultaneous electroencephalograms and electromyograms in patient H.R. A. Patient relaxed. B. Patient working calculation. No correlation of two rhythms. Note increase in amplitude of muscle rhythm with mental effort.

younger group or demonstrate arteriosclerosis in the older one. Cases that did not have tremor were not studied. About half of the patients were not taking hyoscine or stramonium when studied; nine of these were observed again when on hyoscine or stramonium. The rest were taking one of these drugs.

METHOD

The apparatus was a two-channel push-pull set of amplifiers as described by F. and E. Gibbs, made by A. Grass of the Harvard Medical School. The power amplifiers fed into a two-pen ink-writing oscillograph capable of following frequencies up to 120 per sec. with three-paper speeds (1.5 cm., 3 cm., and 6 cm. per sec. respectively). The electrodes for both skull and muscle were small solder discs, 6 to 10 mm. in diameter, fused onto No. 32 enamelled copper wire. These were fastened on with electrode paste and adhesive or collodion placed over the electrode to hold it securely in place. The patients were usually recumbent, but a few were in an armchair with a head rest. The room was not sound proof. The patient was examined both with his eyes closed in the dark, and also with eyes open in the light. The usual procedure was to ground the muscle channel to get rid of the cardiac potentials and record the electroencephalogram on push-pull. Records were commonly obtained from six skull points; right and left occipital, motor, and frontal areas. For the

comparison of electroencephalogram with electromyogram in this series, the contralateral motor area was used unless otherwise specified. Simultaneous tracings from different extremities and from different muscle groups in the same extremity were also made. Records of both monopolar and bipolar leads were made.

Observations

Before regarding the recorded potentials from the intact skull as due to currents from the nervous system, it is extremely important to exclude the artifacts that may occur. Eye movements, muscle potentials, electrocardiographic tracings are now familiar enough to be identified and discarded. We

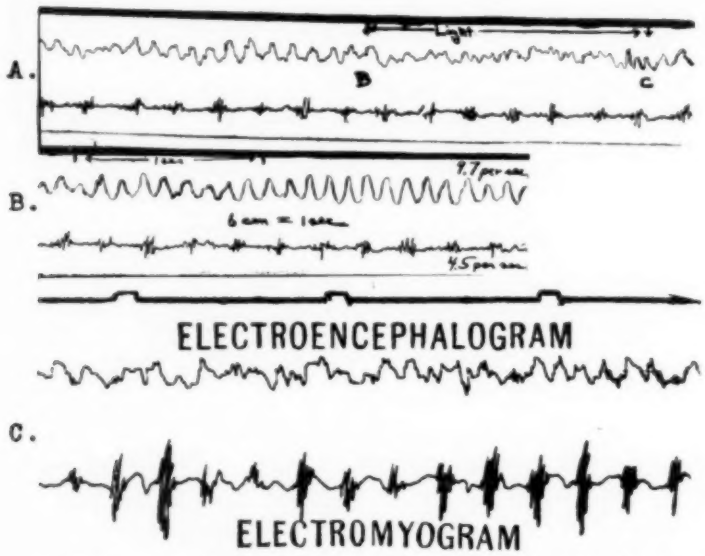

Fig. 3 A. Patient in dark, with eyes open, showing block of alpha waves by light from B to C, and showing no effect on tremor rhythm.

B. Same patient as A, in dark, with eyes closed, showing more marked alpha rhythm. No correlation in muscle and parietal cortical waves.

C. Another patient, showing no correlation between electromyogram and electroencephalogram.

noted in severe cases involving all extremities with obvious movement of the whole body at times, that spikes appeared in the tracing from the head leads which were synchronous with the tremor rhythm. Other observers have believed such spikes to be caused by cortical potentials related to paralysis agitans. We believed that they might be artifacts due to mechanical movements of the head electrodes set up by the tremor, (Fig. 1B). Electrodes on the chin or bridge of the nose in these severe cases produced this same sort of tracing indicating that the tremor spikes were artifacts. In order to confirm our suspicions in the same case as shown in Fig. 2, simultaneous chin and head leads were run into the two channels and the tremor of the arm recorded mechanically by means of a key and the timing pen. All three tracings showed synchronous spikes, proving them to be mechanical artifacts, whereas the

brain wave in this same case was of normal alpha rhythm when the head was quiet (Fig. 1C).

In none of our 37 cases were cortical waves synchronous or in any sort of phase relation to the Parkinsonian tremor of the rhythm. In 4 of the cases we found the head tremor artifact in the cortical leads at some time, and saw it disappear when the head was quiet. The cortical rhythms varied from 10 to 25 per sec., sometimes spontaneously or following bright light stimulus or emotion. The rate of the Parkinsonian tremor, however, remained relatively constant, and the maximum change per sec. being only 6 per cent, *e.g.*, from

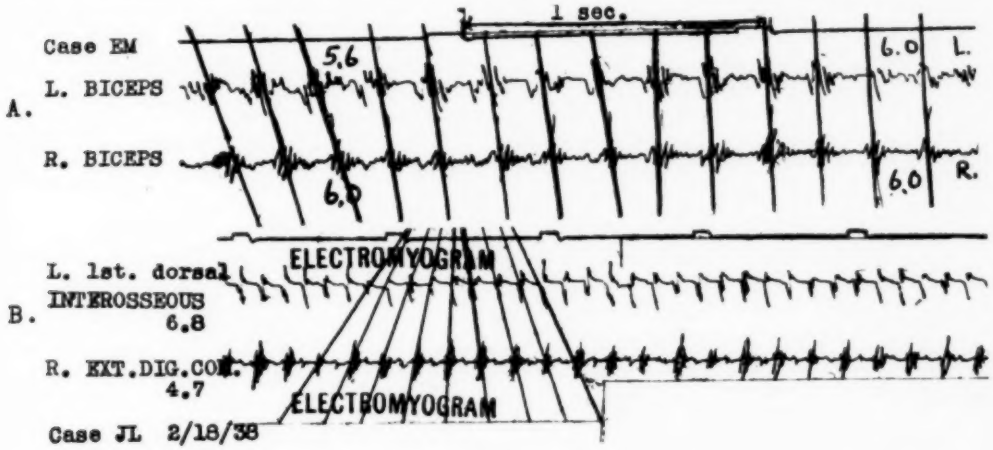

FIG. 4. Simultaneous electromyograms on two different muscle groups. A. Patient E.M., showing a period of asynchronism followed by a period of synchronous discharge. B. Patient J.L., showing complete lack of synchronism, even on repeated runs.

4.2 to 4.5 per sec. With rest and relaxation the cortical rhythm tended to decrease in rate and increase in amplitude, whereas the muscle tremor decreased in amplitude and did not significantly change in rate (Fig. 2A and B). If the average of the cortical rhythm in each case is plotted on a graph against the simultaneous average of the muscle rhythm, there is no correlation whatsoever (Fig. 5).

This study also showed that if careful counts of the tremor are made over 10-sec. periods, the tremor is not of exactly the same rate in two extremities, or even in two independent muscle groups in the same extremity (Fig. 4). Variations in one muscle group of 10 per cent (from 4.1 to 4.6 per sec.) could be found in an hour's observation. The cortical rhythm is more variable and shifts more often. Furthermore, the rate of the cortical potentials is not only different from the tremor rhythm, but bears thereto no simple numerical ratio. For example, if a patient relaxes, the amplitude of the muscle tremor diminishes and may even disappear for short periods, but there is no demonstrable change in cortical potentials, (Fig. 2A and B). On the other hand bright light or opening the eyes may change the cortical potentials without affecting the muscle tremor (Fig. 3A and B).

Discussion

In 1922 Cobb[1] studied the rate and form of the tremor in paralysis agitans by means of a string galvanometer. He considered the rate to be remarkably steady for any one individual regardless of the size or location of the muscle under observation. Since the movements of the galvanometer string were recorded on short strips of film, extensive counts were not possible. In the present study, using an ink-writing oscillograph that permits observation of

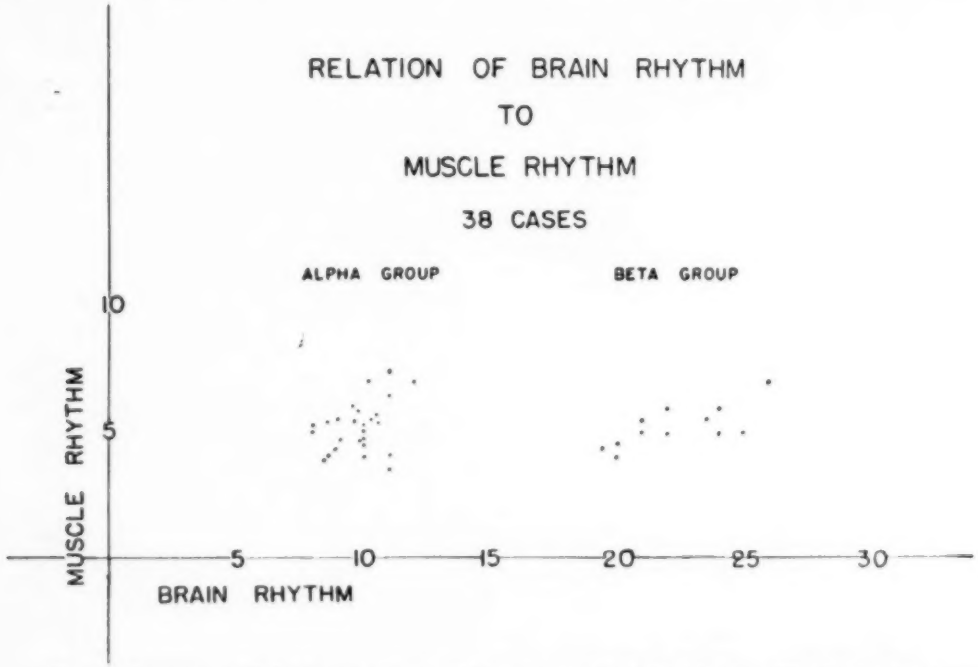

Fig. 5. Summary of the average rate of 10 sec. counts of the 38 cases. The brain rhythms are plotted along the horizontal line and form two groups of waves, the alpha (10-cycle) and beta (24-cycle). Muscle rhythms are plotted along vertical line. No correlation exists.

many yards of paper at a time, significant variations in the rate of the tremor of one muscle were found, and in two different muscles observed simultaneously. These variations are slight, but definite. Similar variations were observed by Herz[2] in 1931 by making cinematograph records of the trembling limbs of patients with paralysis agitans.

Recently, Jasper[3] has published data which he considers proof of the synchronism of the cerebral and muscular potentials in paralysis agitans. The observations described above and shown in Fig. 1B and C. we believe, explain these synchronous waves of Jasper as an artifact. This may also explain the slow waves observed by Yeager and Baldes.[4] If the potentials in the cerebral cortex and in the peripheral muscle were synchronous, one might postulate that the tremor had its origin in the cortex of the fore brain. Our data suggest that the tremor does not originate in the cortex, but in some nervous structure

at a lower level. Since lesions in the motor nerves and in the motor tracts of the cord abolish the tremor of paralysis agitans, our electroencephalographic observations indicate the origin of the tremor lies in some nucleus of the brain stem or basal ganglia.

Conclusion

In 37 cases of paralysis agitans simultaneous electroencephalograms and electromyograms failed to show any relationship between the two rhythms.

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TEMPERATURE CHANGES IN THE CORTEX AND HYPOTHALAMUS DURING SLEEP*

H. M. SEROTA
Department of Physiology, University of Chicago

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THE EXISTENCE of a "sleep center" is now established by animal experiments and clinical data supplemented by necropsy material. The localization of such a center has been much studied and the literature, adequately reviewed by Rowe, places it in the diencephalon, in the hypothalamus, or in the floor of the third ventricle. The mechanism of its function, however, has received little attention. Hess (1931, 1932) has stimulated the sleep area electrically through fine platinum electrodes embedded in the brains of otherwise normal animals and elicited true sleep, easily repeatable in the same animal. On the basis of this and other observations, such as pupillary constriction and increased intestinal mobility during normal sleep, he postulates the existence of a parasympathetic center which, by increasing its activity, leads to sleep. This implies the discharge from it of sleep-producing impulses.

In the human (Fulton and Bailey, 1929) and the cat (Ranson, 1934), however, sleep and somnolence are the usual outcome of destructive lesions in the same area. Further, Ranson has elicited rage reactions rather than sleep by hypothalamic stimulation. The seeming conflict in producing sleep by stimulation or destruction of a localized "sleep center" demands further study. It is conceivable that an actively functioning sleep center should manifest an increase in metabolism while other regions, *e.g.*, the cortex, show a decrease during sleep. The technique devised for the localization of thermal changes in the cat brain (Serota and Gerard) was therefore adapted to the study of this problem.

METHOD

Twenty-six cats were operated on aseptically under intraperitoneal nembutal anaesthesia, and two or three thermal needles inserted into the brain with the aid of the Horsley-Clarke instrument. Through small skin incisions and narrow drill holes the needles were lowered to the proper depth and then secured by sterile wooden wedges, dental cement, or Duco cement, spread uniformly within a hollow brass screw. The animal was allowed 18 to 24 hours recovery before study. Post-operative pain or infection was minimal, and most animals were active and ate within a day or a day and a half. Only docile cats with like weight and skull characteristics were used.

Thermocouples were made of 38 gauge enameled copper and constantin wire and were further insulated at the bared junction with Duco cement or Bakelite varnish. The extracalvarial portion was covered with waxed linen, rubber, or gutta percha to guard against fortuitous fluctuations in environmental temperature. These insulated wires were connected to binding posts on a cap or collar fixed on the animal. From these, low resistance cables of the same wire connected the constantin, through a constant temperature junction, and the copper, directly, to the galvanometer circuit. The resistance of the thermocouples was 25 ohms, that of the galvanometer, 30 ohms. The sensitivity used in these experiments was 10 mm. =0.1°C., the galvanometer being slightly overdamped. While the

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animal behaved in a normal manner, pacing about the cage, eating or sleeping, temperature readings of each area were made every 3 minutes, the shift from one thermoneedle to another requiring only 15 sec. The hypothalamic lead was placed within the following boundaries (Ranson): 6 to 12 mm. anterior, 0 to −5 mm. vertical and 1 to 4 mm. lateral. The cortical leads were variously inserted in the suprasylvian, lateral, and splenial gyri, from 16 anterior to 2 mm. posterior to the interaural plane, and from 2 to 5 mm. below the dura. The position was checked by gross section.

The criteria of sleep were: the assumption of the "sleep position" (LDCU, *i.e.*, lying down curled up, Fig. 1), and its maintenance for at least 20 minutes; respirations fewer than 20 per min.; few full-bodied movements or changes of position; and refractoriness to noise (*e.g.*, no response to dropping a metal weight on the table). By all these tests an animal nearly always slept shortly after a satisfying meal. Other occasional "naps" or resting periods were easily excluded.

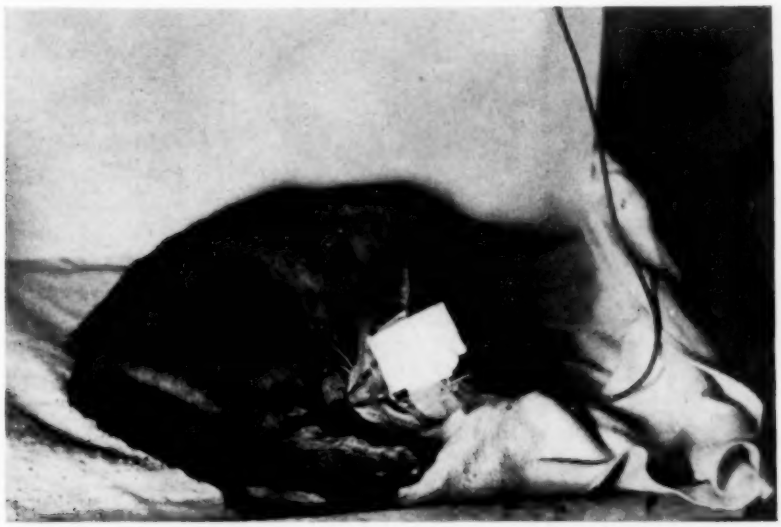

FIG. 1. A typical variant of the "sleep position" in which the animal lies down curled up, "LDCU." (Photographed by Dr. L. L. Robbins.)

RESULTS

The hypothalamus is consistently 0.1 to 0.5°C. warmer than the cortex. This difference fluctuates considerably during the waking state but remains positive at all times. While the animal paces about the cage, sits, cleans itself, or eats, the temperature curves of these areas rise and fall as much as 0.2°C. The variations plot an irregular saw-toothed curve, each tooth lasting from 6 to 12 min. and at times recurring in a definite rhythm or coincident with gross skeletal movements, (Fig. 2). Other more regular temperature changes accompany definite behavior. Thus, during the obvious excitement which follows the sight and smell of food, the temperatures of both hypothalamus and cortex rise, but the former increases more. When food is eaten, both temperatures drop, and the change in the hypothalamus is again greater. (The temperature drop is a direct cooling effect of the food on the blood, for eating warm food leads to a rise.) Defecation and urination also result in a temperature fall. When the animal lies or crouches, both temperatures fall.

In all of these instances both structures appear to change temperature simultaneously.

During the somnolence which frequently follows a meal, while the animal nods and crouches, the temperature curves become irregularly rhythmical, both the temperatures and their difference (hypothalamus minus cortex) rising and falling by 0.1°C. over intervals of 6 min. Prior to the assumption of the "sleep position" there is usually a rise in the hypothalamic temperature, and when the animal curls up on its side and sleeps both the temperatures and the difference between them fall and the jags on the curve are replaced by a reflectively flat plateau (Fig. 2). The hypothalamic temperature may drop

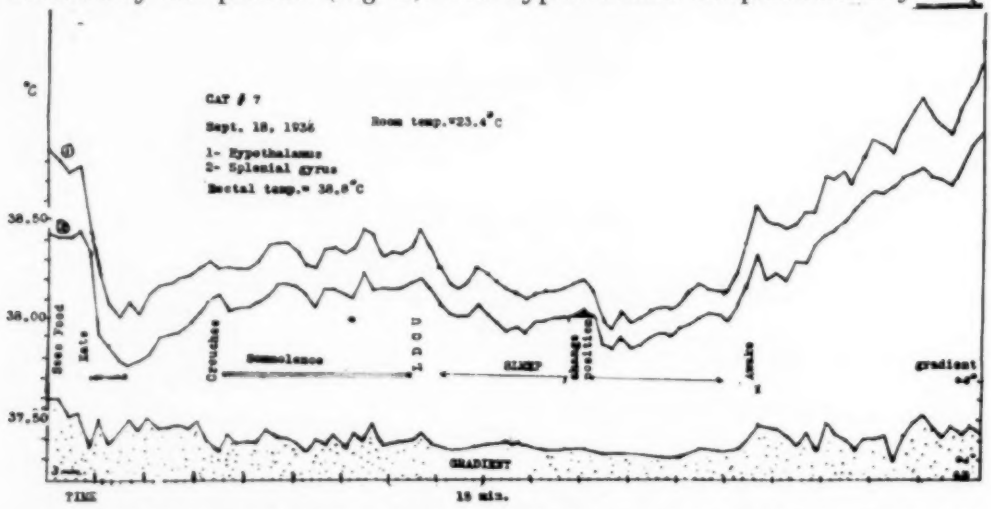

FIG. 2. Characteristic findings in sleep. Ordinate, temperature in degrees Centigrade; abscissa, time in 15 min. intervals. Two thermocouples, a cortical and hypothalamic, are simultaneously followed at 3 min. intervals. LDCU represents assumption of the "sleep position." Curve 1, absolute temperature of the hypothalamus; 2, same of the cortex. The stippled area is the temperature difference between them.

as much as 0.4°C. and the cortical only 0.2, so that the difference is reduced by 0.2°C. On waking the changes are reversed, and frequently a temperature increase, seen first in the hypothalamus, precedes the other signs of arousing.

The greater fall, during sleep, of the hypothalamic temperature than that of the cortex is not shared as markedly and consistently by other structures. Thus, a third needle in Ammon's horn or in the tail of the caudate nucleus showed a smaller temperature change than the hypothalamic needle. (These structures are at a depth equivalent to that of the hypothalamus and serve to control any effect of sleep on the pre-existing gradient (Serota and Gerard, 1938). Not all curves fitted the above description. Thus, of 119 curves on 26 animals, 88 showed a fall during sleep, 18, a rise, and 13, no change. About the same proportions hold for each lead. In 80 cases the curve flattened to the typical plateau, sometimes with a rise of temperature. On comparing hypothalamus and cortex the temperature in the former decreased relative to the latter in 31 cases out of 37 and rose in only 1. The temperature of the cornu

and caudate, in contrast, fell relative to that of the cortex in only 7 and rose in 3 cases out of 14.

To determine to what extent the specific cooling of the hypothalamus in sleep was due to diminished metabolic activity of its cells or to change in blood supply, the heated thermo-junction of Gibbs (1933) was used. This responds to greater blood flow by a drop in temperature larger than any changes in the unheated needle (Serota and Gerard, 1938). The heated needle

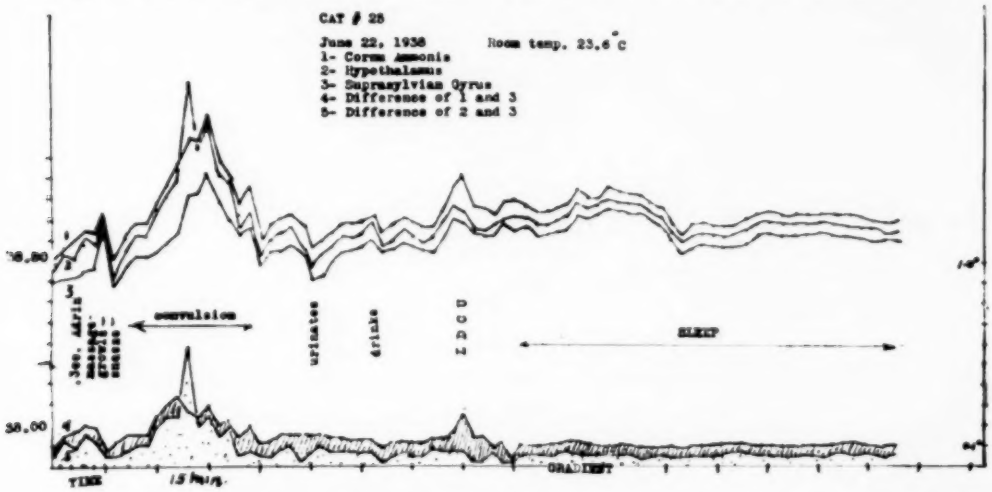

FIG. 3. Minor convulsion induced by epinephrin injection. Ordinate and abscissa as in Fig. 2. The temperature changes recorded by three thermocouples placed in the Cornu Ammonis, the hypothalamus, and cortex, are followed in curves 1, 2 and 3 respectively. Curve 4 represents the temperature difference of curves 1 and 3; and curve 5, of 2 and 3. Following the subcutaneous injection of epinephrin a period of hyperkinesis, ataxia and hypertonia results. This is succeeded by normal behavior and then by deep sleep.

showed only a slight temperature fall during sleep, indicating an insignificant change in blood flow. The validity of this conclusion was further checked by finding that eating either warm or cold food, which increases blood flow, cooled the heated needle, though the unheated needle was warmed or cooled, respectively, by warm or cold food, and by a smaller amount.

It follows that the hypothalamic neurones decrease their activity in sleep. It might be anticipated that in excitement the reverse would occur. Confronting a cat with a barking dog elicited in it the usual emotional storm and increased all brain temperatures, that of the hypothalamus most. A similar stimulation by epinephrin (0.3 cc. of 1–1000 Adrin subcutaneously, followed by local massage) caused hypertonia, ataxia and hyperkinesis amounting to a mild convulsion, and lack of response to a threatening gesture before the eyes. Subcortical temperatures rose more and sooner than that of the cortex and paralleled the motor symptoms, the hypothalamic temperature outstripping the others at the moment of most violent hyperkinesis. As the temperature difference between cortex and hypothalamus subsided, the convulsion ceased, the animal defecated, urinated, ate in the usual manner, lay down, and fell

into an unusually deep sleep (Fig. 3). (Compare the silent period of the EEG after an epileptic discharge.)

Hypothalamic temperature and not others, would frequently rise over a period of 3 to 12 min. during sleep and at its maximum the animal would suddenly shift position. Temperature then fell at once with the attainment of the new position. This continual accumulation of "tension" during sleep, released in muscular movement, has frequently been pointed out (Kleitman, 1929). The hypothalamus apparently plays a role in the discharge of these tensions.

Discussion

The constant alteration in brain temperature during sleep is a smoothing off of the jagged activity curve and a fall in hypothalamic temperature greater than elsewhere. Exceptions occur: the plateau may be broken due to restless sleep with much movement; and a preceding cold meal may have lowered brain temperature before sleep so much (1.0°) that it continues to rise even when sleep sets in. Still other irregularities occur uncommonly and are not explained.

The fall in temperature is not attributable to changed blood flow, as shown above. Gibbs (1935) also failed to find an altered flow in the human jugular during sleep. An increased heat loss from the brain through its coverings (Serota and Gerard, 1938) would affect cortex far more than deeper structures, which is not the case. The only satisfactory explanation of the cooling is a decreased heat production due to diminished neurone metabolism. The findings of Lampl and Feitelberg (1935) further indicate this. A thermocouple in the cat's cortex registered 0.5°C. warmer than that in the carotid artery during ordinary waking activity, 0.2° warmer during rest, and actually lower under paraldehyde anaesthesia.

The greater fall in hypothalamic than in other brain temperatures during sleep indicates a specific diminution of activity of these centers. This is in accord with the findings of Ranson (1934) and of Bard (1928), who found that stimulation of the hypothalamus leads to increased general activity, and indicates that sleep is associated with depression of the hypothalamus rather than its stimulation. The apparently opposed findings of Hess (1931) may perhaps be due to a depression rather than a stimulation of the "sleep center" by the sleep-producing slow currents used by him. Certainly the induction of sleep in his preparations by the injection of ergotoxin into the third ventricle is more easily explained by the view advanced above.

The technique of chronic temperature measurements of local brain regions obviously lends itself to many uses. For example, benzyl-methyl carbinamide (Benzedrine, 10 mg. subcutaneously) has been found (Serota and Schreider, unpublished) to increase temperature in all brain areas studied. The irregularities are supplanted by a smooth parabolic curve which rises and falls symmetrically over a period of four to eight hours, during which time the animal shows minimal increase in motor activity but marked decrease in threshold to faint light or sound stimuli. Serota and Gerard, in preliminary experiments,

have found no evidence of a differential depression of either cortex or thalamus during the anaesthetic action of ether, nembutal, etc.; though all narcotics markedly lower brain temperature in relation to general body temperature.

Conclusions

A technique is presented for following the temperatures of local brain regions in the unanaesthetized cat.

In the conscious, as in the anaesthetized animal, basal brain regions are warmer than the cortex. Absolute temperatures fluctuate during the waking state, sometimes in a semirhythmic manner, and the positive temperature difference between hypothalamus and cortex increases in irregular fashion with activity.

Emotional states, as fear, rage, or anticipation of food, increase the relative temperature of the hypothalamus; sleep, especially, decreases and stabilizes it.

On awakening from sleep, hypothalamic temperature rises earlier and further than that of the cortex, caudate nucleus, or Ammon's horn.

The specific temperature decrease of the hypothalamus in sleep is shown to be due to lowered cell metabolism rather than to any marked change in blood flow. This indicates that sleep is associated with a decreased rather than an increased activity of a hypothalamic "sleep center."

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FACTORS INFLUENCING BRAIN POTENTIALS DURING SLEEP*

HELEN BLAKE, R. W. GERARD, AND N. KLEITMAN
From the Department of Physiology, University of Chicago

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LOOMIS, HARVEY, AND HOBART (1937) have divided the period of sleep into several stages on the basis of changes in human brain potential patterns; Davis *et al.* (1938) have further analyzed the changes during the first part of the night; and Blake and Gerard (1937) have found delta wave intensity to parallel depth of sleep as determined by response to an auditory stimulus. Many bodily states show diurnal variations, for example: consciousness, movement, autonomic tone, skin resistance, and temperature (Kleitman, 1929). Some of these factors, as well as certain abnormalities in sleep, such as narcolepsy and sleep after experimental insomnia, have now been studied in relation to brain potentials in an attempt further to elucidate the mechanisms involved in the reversible change from wakefulness to sleep.

METHOD

Small silver (or solder) bipolar disc-electrodes, fastened to any two regions of the scalp (by collodion), were used to lead off the brain potentials in some experiments; more often monopolar leads were used consisting of a ring on the ear lobe and a disc on the vertex or occiput. Two independent, five-stage, resistance-capacity, push-pull amplifiers (time constant = 0.5 sec.; Offner, 1936) fed cathode ray oscillographs and crystographs (Offner and Gerard, 1937).

Depth of sleep was measured as before by the duration of a constant sound required to elicit a response from the subject. Movement was measured by a motility box (Kleitman, 1932) and by muscle potentials picked up in the head leads. The latter was a more sensitive index, the record consisting of periods of muscle tension rather than of gross movements, and sometimes gave indication of changes not detected by the motility box. Temperature was taken orally. The subjects were usually placed on a bed in a darkened room, quiet except for the constant hum of a motor; but in one series of narcoleptics the subjects sat in an upright position and with ordinary illumination. Twenty-two experiments were performed on 8 normal adult subjects and 30 on 11 narcoleptics. One normal subject was studied during wakefulness and sleep after 100 hours of continuous experimental insomnia.

RESULTS

Factors in normal sleep

Comparison of leads. We have corroborated the findings of Loomis *et al.* (1937) and Davis *et al.* (1938) that during sleep the 10 per sec. trains are more often present at the occiput and the 14 per sec. rhythm at the vertex, and that the amplitude of the 1–3 per sec. waves is greater at the vertex. But, despite such detailed differences, all potentials are present over the entire cortex. When potentials from two head regions are compared, similar patterns of delta waves are clearly simultaneous at the parietal, occipital, frontal, and temporal regions, bursting into activity and subsiding suddenly (see also

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Loomis *et al.*, 1938). Further, whether or not the 10 per sec. rhythm is present in all regions at a particular time, all leads may show bursts at this frequency at some stages of sleep. With leads from only the occipital and frontal regions, Blake and Gerard found the 14 per sec. rhythm inconspicuous; with the vertex lead it is now clearly seen, even without specially tuned circuits. The fraction of the time during which the 14 per sec. rhythm is present increases slowly, and with fluctuations, during the early part of the night (alpha+delta period, see below), reaches a maximum in the middle portion, and declines gradually as the alpha waves again appear. The amplitude of the rhythm is lowest in the period during which the slow waves predominate (compare Davis *et al.*, 1938).

Table 1. Potentials in stages of sleep

	Amt. Alpha	Amt. Delta	Amt. 14 per sec.	Depth of sleep	Present Nomenclature	Nomenclature of Tuxedo Park Group*
1	++	−	−	Awake	Alpha	A. Interrupted alpha B. Low voltage C. Spindles
2	+	++	+	Light sleep	Alpha+delta (+14 per sec.)	
3	−	+++	+	Deep sleep	Delta (+14 per sec.)	D. Spindles+random E. Random
4	−	−	+	Light sleep	Null (or low voltage)	B. Low voltage
5	(+)	−	(+)	Sleep to wake	Intermittent alpha	B. to A. Low voltage to interrupted alpha
6	+	−	−	Awake	Alpha (low intensity)	

* The nomenclature of the Tuxedo Park group represented above is the result of personal communication with Dr. E. N. Harvey and Dr. H. Davis.

Sleep stages. Loomis *et al.* (1937, 1938), using tuned and untuned circuits, have described five stages of sleep: A, alpha; B, low voltage; C, spindles; D, spindles+random; and E, random. Potential patterns corresponding with these stages have been observed in the present experiments but others are also evident. The changes of potential pattern in the course of the night seem best described in terms of the combined curves of rise and fall of each individual rhythm. Despite the large and frequent fluctuations from one potential pattern to another (Blake and Gerard, 1937; Loomis *et al.*, 1937), especially when the subject is disturbed, there is a definite slow shift through the night in potential pattern prominence. This has been evaluated for the two faster rhythms, as previously for the slow one, by averaging the dominant potentials over 5 min. periods through many nights of sleep. Curves illustrating the per cent presence of alpha, delta and 14 per sec. rhythms are shown in Fig. 1. Fluctuations lasting 2 minutes or less (due to extraneous sound stimuli, etc.) are not considered.

This set of curves permits a description of potential changes during the night. The major patterns are presented in Fig. 2. This arrangement does not conflict essentially with the stages of Loomis *et al.* (1937) and seems preferable since it is based upon the quantitative measure of per cent presence of each type of wave rather than upon the more qualitative recognition of certain potential patterns. For convenience, the generally accepted, although perhaps misleading, convention has been used of assigning a letter to each wave fre-

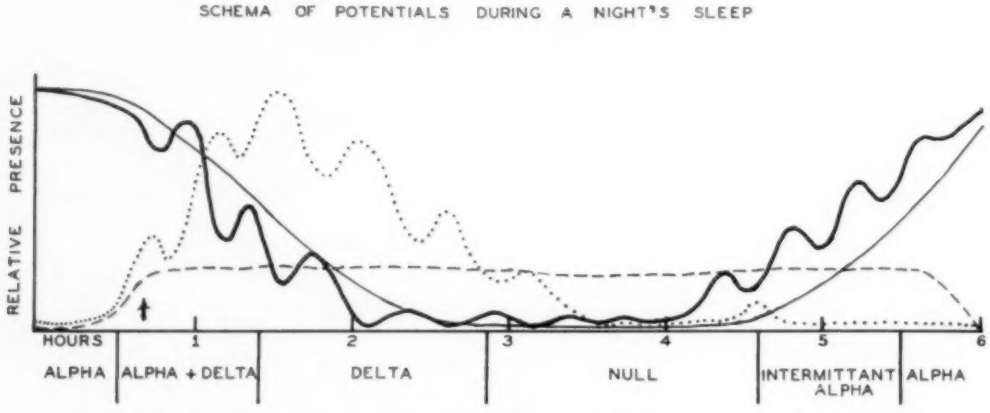

FIG. 1. Predominance of brain potentials through the night. Alpha waves (black heavy line) in per cent presence; 14 per sec. waves (dashes) in per cent presence and delta waves (dots) in extent of predominence. Oral temperature (black thin line). Below the stages of sleep are indicated. Record begun at time of retiring arrow indicates beginning of sleep. Wavy lines represent changes in waves due to shift of state of sleep. Depth of sleep by auditory response method roughly parallels delta curve.

quency. "Alpha" stands for the 10 per sec. regular rhythm usually present during the waking state. (In cases where the beta waves are the normal resting potentials, beta would replace alpha. "Alpha+delta" would be replaced similarly by "beta+delta.")* "Delta" is used for the 0.5 to 5 per sec. sometimes irregular wave dominant in deep sleep. The period of light sleep in the third quarter of the night, when delta waves have disappeared and the flat base line is broken only by an infrequent slow wave, or by a burst of alpha or beta waves, is called "null" (or low voltage) (Table 1).

The changes during diminishing sleep in the late part of the night fail to mirror those of increasing sleep in the early part in the following respects

* Personal communications from Drs. Harvey and Davis have brought up the question whether the 10 per sec. rhythm seen simultaneously with the delta rhythm in the "alpha+delta" period is the same as the 10 per sec. wave of wakefulness or whether it is the beta component which has been slowed from 25 to 10 per sec. This question cannot be answered from the present work. It seems clear that the 10 per sec. rhythm in this "alpha +delta" period is not so closely associated with consciousness as it is later in the night (see below) and may, therefore, have a different significance. On the other hand, normal "beta" subjects show a "beta+delta" stage in contrast to the more common "alpha +delta"; and notched waves at this stage in the alpha case seem to be in transition between alpha and delta.

(Fig. 2): (i). The delta component reaches a peak in the second hour of sleep, then gradually disappears in another hour or two. (ii). The delta waves first appear before the alphas disappear, producing "notched" waves (Fig. 2b; also Blake and Gerard, 1937); whereas later the deltas fade some hours before the alpha waves return, leaving an essentially flat base line. (iii). The alpha waves are 20 to 40 per cent larger and the betas more prominent and of higher frequency just before falling asleep than just after awakening. (iv). Consciousness is associated with the presence of alpha waves in the "null" period but

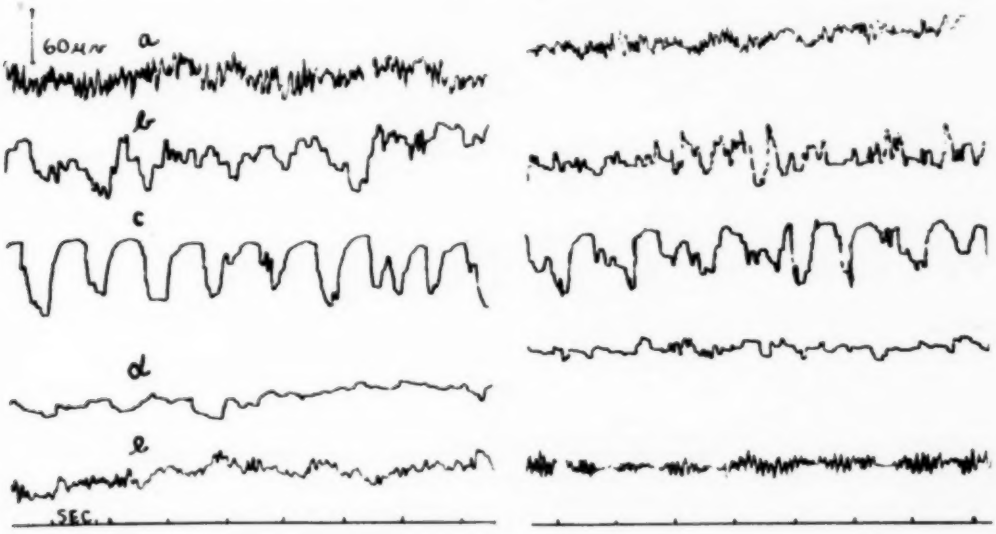

FIG. 2. Potential patterns through the night on three subjects. 1. "Alpha" rhythm of wakefulness. 2. "Alpha+delta" period of light sleep. 3. "Delta" period of deep sleep. 4. "Null" period of light sleep. 5. "Alpha" rhythm of wakefulness.

not necessarily in the earlier "alpha+delta" period. (v). Weak stimulation, such as slight movement or noise, affects brain potentials, particularly the delta rhythm, oppositely in the early and in the late period of light sleep (Loomis *et al.*, 1937; Blake and Gerard, 1937). In the "alpha+delta" stage it usually diminishes the delta waves, which emphasizes the alphas. In the "delta" and early in the "null" stages, a similar stimulus either exaggerates the slow waves already present or initiates them and also a faster rhythm, which last for a few seconds. This corresponds to the "K complex" of Loomis *et al.* (1938). Later in the "null" stage stimulation causes alpha waves to appear. It seems, then, that a stimulus which produces a shift towards lighter sleep causes the potentials present at the time to pass through those of the preceding stage before reaching the alpha waves of wakefulness.

Consciousness. The relation between consciousness and brain potentials was investigated by Davis *et al.* (1938) by having the subject squeeze a bulb when aware of having "drifted off." They found that alpha waves, which were absent during a "float," had returned between 3 and 23 sec. before the

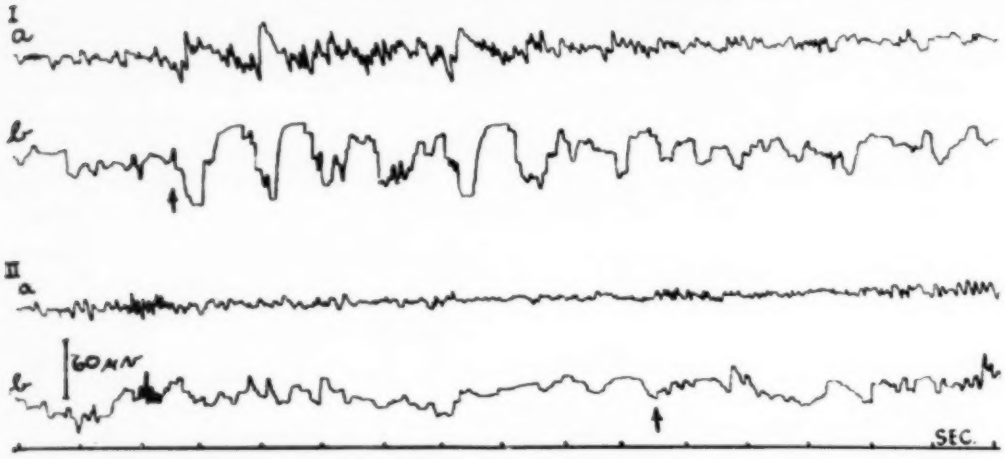

FIG. 3. Effect of slight stimulation (at arrows) on brain potential pattern: 1. As the delta waves are diminishing after deep sleep. a. Low cut-off filter in, b. No filter. 2. Late in the "null" period. a. Filtered. b. Unfiltered. Note that whereas in the first record stimulation elicits a train of delta waves, later it does not.

signal was given. We have studied the loss rather than the return of consciousness and related it to dreams and to skeletal muscle tonus.

A. *Dreams.* Loomis *et al.* (1936) at first suggested that dreams were associated with a "peculiar" slow wave, but later (1937) decided that they are not associated with any particular wave but occur in the B stage of sleep. Davis *et al.* (1938) find dreaming also in the C stage. In the present experiments, the subject was suddenly awakened while some particular wave pattern was present, and asked whether he had been asleep and, if so, whether and about what he had dreamed. Some individuals did not show sharp potential changes from one sleep level to another and others found it difficult to decide clearly whether or not sleep and dreams had been experience. In all subjects

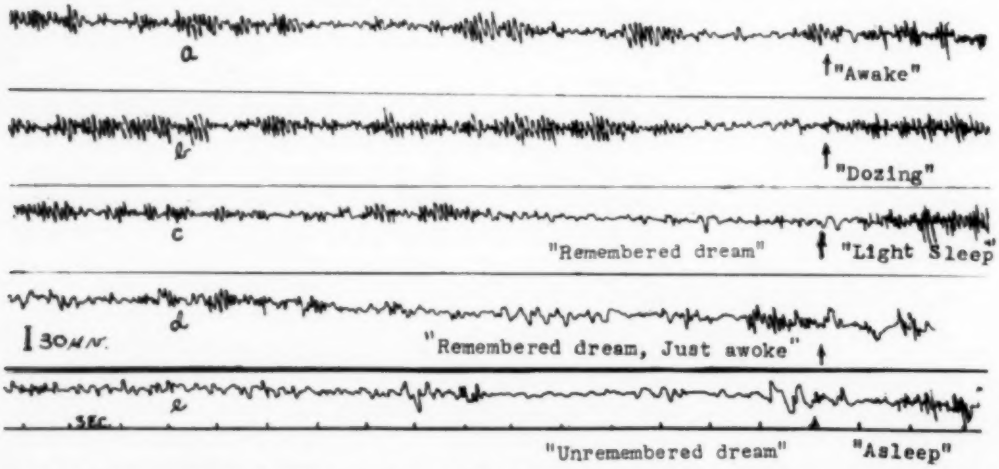

FIG. 4. Record in the "null" period of light sleep with low cut-off filter. Subject was awakened and questioned about dreaming at the arrow.

a uniform general correlation between potentials and dreams was present, but the following details are based largely upon results obtained on one young woman able to give decisive subjective reports (Table 2, Fig. 4): (i) Report, "awake." In the "null" period, the presence of alpha waves, even for one second, was invariably associated with a report of consciousness. (Fig. 4a); (ii) Report, "dozing"—some dimming of awareness and decreased sense of reality of surrounding events. This was the report when alpha waves had been absent for at least 3, average 6, sec. (Table 2). (iii) Report, "remembered

Table 2. Brain potentials and introspection during sleep in second half of the night (one subject)

Subjective Impressions	Duration of period with no alpha		Presence of delta	Number of queries
	Average sec.	*Range* sec.		
Wakefulness	0	—	−	6
Dozing	6	3–7	−	7
Remembered dream	9	2–16*	−	15
Unrecalled dream	55	6–120	+	6
Dreamless	?	?	+	Rarely occurred

* In one case there were no alpha waves for 150 sec. before the query but this is the exception; the usual figures are close to 9 sec.

dream"—light sleep with a dream clearly remembered. In nine-tenths of the trials, when alpha waves had been missing for 9 sec. (and no delta waves were present) the subject could remember a dream. (iv) Report, "unrecalled dream"—deeper sleep with a clear memory of having dreamed but no recall of content. This was the report when alpha waves had been absent, on the average, for 55 sec. Delta waves were usually present. (v) Report, "dreamless sleep"—deep sleep with no suggestion of having dreamed. This report paralleled a prominent delta rhythm, and rarely occurred in the second half of the night or early in the alpha+delta stage.

The subject was awakened at irregular intervals throughout the night in these tests and it is clear that dreaming was present most of the time, although minimal in the second quarter (delta period). The change from thinking to dreaming, with advancing sleep, seems to be less an immediate depression of mental activity than a progressive shift of attention from exteroceptive sensations towards subjective imagery. Even in deep "dreamless" sleep there is only a short period during which cortical activity is probably depressed to such an extent that the subject is not aware, on abrupt awakening, of having dreamed.

B. *Tonus.* As a test for tonus, the subject held between two fingers a light spool, which fell as the muscles relaxed in sleep. The subject was then aroused and asked whether or not he had been aware of dropping the object. The spool usually fell between 0.5 and 1.5 (average 1.1) sec. after the alpha rhythm had disappeared. The subject was then aware of its fall. Occasionally, however,

the fall was delayed until 6.5 to 25 (average 14) sec. after alpha loss, in which case the subject was unconscious of having dropped it. Tone, therefore, diminishes soon after the alpha rhythm is lost, but consciousness does not disappear for some seconds more. Subjective "dozing," shown above to follow the disappearance of alpha waves by 6 sec., is experienced between loss of tone and loss of consciousness. The subjects of Davis *et al.* (1938) similarly did not consider "floating" or "dozing" as real sleep.

Table 3. Effect of movement on brain potential patterns

Type of brain wave change	Duration of movement (sec.)	Duration of brain wave change (sec.)	Number of movements
$\alpha+\Delta\rightarrow\alpha$	21	14	6
$\Delta\rightarrow\alpha$	22	24	13
null $\rightarrow\alpha$	19	28*	20

* Several times changes, not included in the table, lasted for minutes and the level of sleep was permanently changed.

Motility. Blake and Gerard (1937) found that movement was regularly associated with a shift to lighter sleep. Loomis *et al.* (1937) report that "Movement may occur without a change of state (of sleep) and a change of state without movement, but frequently movement is immediately followed by a change of state upward, occasionally downward. . . ." In 90 per cent of movements in which muscle tension lasted over 5 sec. (80 instances now analyzed in detail) brain potentials shifted to a pattern of a lighter sleep; in 10 per cent they did not change, mainly in the null period. There was no shift towards a deeper level. (A transient increase in synchrony of delta waves in the third quarter of the night is evidence of decreased depth of sleep; cf. above.) Average values for the duration of movement (about 20 sec.) and the direction and duration of potential changes (progressively longer from the "alpha+delta" through the "null" stages) are given in Table 3. Occasionally sleep would remain lighter for over an hour following a movement. In some 5 per cent of all observations, alpha waves appeared before movement occurred, suggesting that extero- or interoceptive stimuli were responsible for the change; and even when brain and muscle activity were simultaneous such stimuli may have lightened sleep sufficiently to permit proprioceptive reflexes to break through. Certainly after movement is initiated the new proprioceptive barrage would tend to cause awakening.

Temperature. Alpha frequency varies with temperature in the waking subject (Hoagland, 1936; Jasper, 1936). The diurnal temperature change, 0.5°C., would only account for a frequency change between 10 and 9.7 per sec., assuming the mu value of 7000–8000 cal. (Hoagland). There is a 10–20 per cent slowing of the alpha rhythm with the onset of sleep (Davis *et al.* 1938) and a further diminution through the night, in close parallel with the amount of tremor (Jasper, 1938). We find the per cent presence of alphas parallels the temperature curve during sleep rather closely as both fall to,

and maintain, a low level, while only late in the "null" period does the alpha curve rise in advance of that for temperature (Fig. 1). This correlation is reasonable since the alpha rhythm is associated closely with tonus. (See above; also Jasper, 1938.) A decline in muscle tone should decrease body temperature gradually; an increase in tone should raise temperature, but not so quickly as it restores the alpha rhythm. Both the alpha rhythm presence and the temperature are lower in the morning after waking than they were the previous evening.

Abnormal conditions

Experimental insomnia. Behavior and potentials during prolonged insomnia and subsequent sleep have been studied (Kleitman, 1923; Blake and

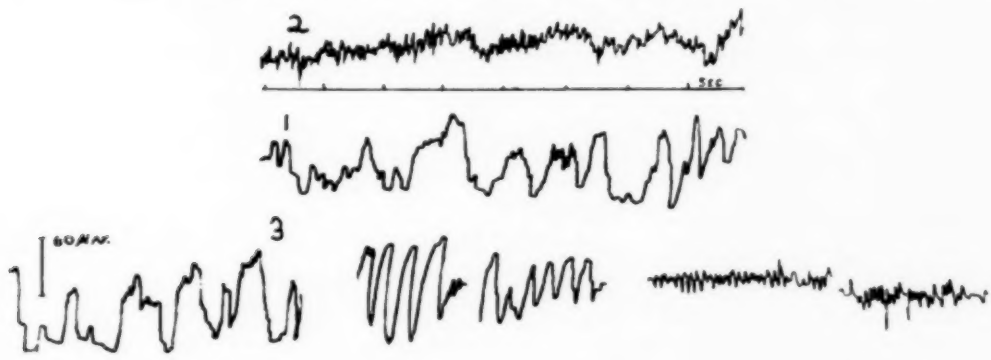

FIG. 5. Record of subject with 100 hours' insomnia. 1. "Normal" record. 2. When subject was trying to concentrate on counting. 3. Several regular potentials appearing within a 5 min. period.

Gerard, 1937). Observations have now been made on one subject, of the dominant alpha type, after 100 hours of insomnia. (Benzedrine was taken at intervals; Kleitman, unpublished.) Slow waves predominated with the subject recumbent, even though talking or with the eyes open, and they disappeared only when he made an extreme effort to concentrate. The 3–5 per sec. rhythms with 14 per sec. superimposed were the most common potentials; but all varieties of slow waves appeared and in no regular sequence with deepening sleep. Muscular tone was so low that even with distinct effort the spool was never held more than 15 sec., and usually it was dropped immediately.

The subject was never aware of having slept and thought he answered every question, but actually a strong auditory stimulus was often required to arouse him to the point of responding, which shows failure to differentiate sleep from wakefulness. To check the maximum duration of wakefulness, the subject counted as long as he could. This required intense concentration and was paralleled by a great discharge of beta waves which displaced the delta rhythm. Even with this effort, consciousness was lost at a count between 3 and 10 and, in about as many seconds, the potentials drifted back to the usual slow ones. Possibly most striking, was the play of many regular rhythms.

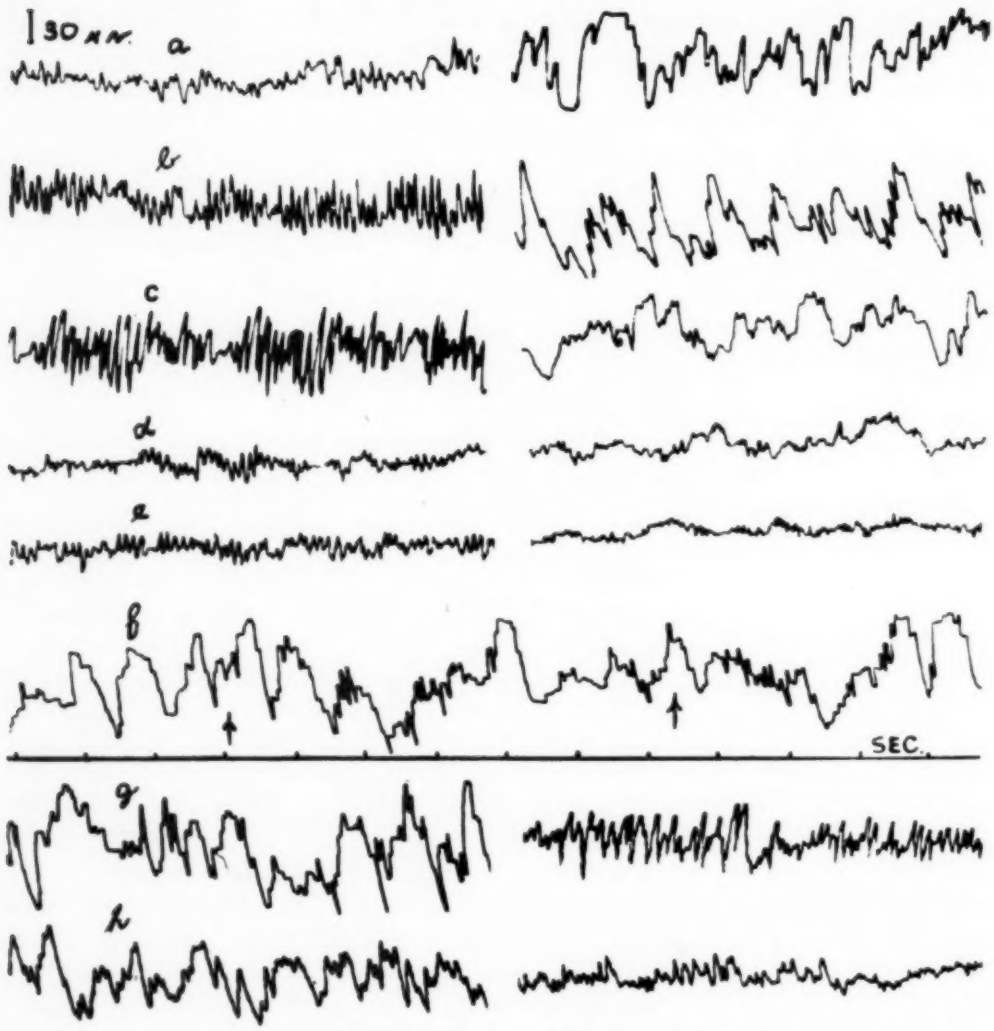

FIG. 6. a, b, c, d, e. Characteristic records of potentials from narcoleptics: 1. Lying down. 2. Sitting up. f. Response of narcoleptic to query in spite of presence of delta waves. g. h. Record of two narcoleptics lying down. Left. Before benzedrine. Right. One hour after 10 mg. benzedrine orally.

Within a five minute period: 1, 2, 3, 10 and 14 per sec. rhythms were clear, besides the high frequency beta discharge (Fig. 5). The genesis of these rhythms will be discussed later.

Narcolepsy. Eleven narcoleptic patients, male and female, of varying ages, were studied for four months during day and night sleep. Two had an associated obesity and one was an alcoholic.* In 10 of the cases a good alpha predominated in the sitting position; but on lying down this was always markedly diminished, and was usually replaced by large delta waves. The change oc-

* We are indebted to Dr. Walter Adams for the opportunity to study these patients. He will report elsewhere on the clinical aspects of this group of narcoleptics.

curred simultaneously in occipital, frontal, parietal and temporal leads, as in normal sleep. Delta frequencies from 0.5–5 per sec. appeared irregularly in each case (Fig. 6), much as in deep normal sleep. This is in contrast to the normal pattern of rest, in which the alpha rhythm persists through hours in the recumbent position, and even to that of day-time naps, in which the alpha rhythm is often merely depressed and delta waves are uncommon (Blake and Gerard, 1937). The correlation between depth of sleep, as determined by the auditory response method, and type of potentials was normal. Some patients characteristically slept deeply, others lightly, but all showed wide variations in sleep level. Since the changes between wakefulness and sleep are marked so clearly in these patients by changes in brain potentials, the electrical method may prove valuable for the objective determination of the frequency and duration of the narcoleptic attacks. It should be particularly useful in stuporous patients for discriminating sleep from simple unresponsiveness.

Drugs (a) *Benzedrine.* This drug is reported (Davidoff and Reifenstein, 1937) to increase wakefulness, excitation, mental activity, metabolism, and sympathetic stimulation, and was found (Blake and Gerard, 1937) to diminish the large delta waves present during sleep after prolonged insomnia. In 10 experiments, benzedrine sulphate (10 mg.) did not obviously affect the frequency or amplitude of the waking alpha rhythm, when psychological factors were controlled. During sleep, however, the delta potentials were diminished in duration and amplitude. This was particularly marked in narcoleptics (Fig. 6).

(b) *Alcohol.* Mullin *et al.* (1937) reported that alcohol increased depth of sleep during the first part of the night and decreased it during the second half. This has been confirmed (4 experiments) and a parallel change in potentials demonstrated, delta waves being accentuated early in the night, alpha waves later. Possibly the early peripheral vasodilatation, and consequent lowering of body temperature, is one factor favoring the early deep sleep.

Discussion

If one defines sleep in terms of loss of consciousness (Kleitman, 1929; Hess, 1932), the light sleep of day-time naps offers a simple case for study of the essential changes. Here the constant alteration is a diminution of the alpha rhythm. Delta waves, or the 14 per sec. rhythm, may or may not appear. Loss of consciousness and of alpha rhythm are related and the alpha rhythm, further, is associated with muscle tone, the two decreasing together. Kleitman (1929) has emphasized the importance of diminution in proprioceptive and other afferent stimuli in inducing sleep and suspending consciousness, so the close relation of alpha waves to both tonus and awareness is significant.

The work of Bremer (1935, 1937) likewise emphasizes the importance of diminished afferent impulses in producing the cortical potential changes of sleep. In the cat, mesencephalic section of the brain stem, barbiturate narcosis, and sleep are all associated with cortical waves of decreased frequency

and increased amplitude. Several workers (Jasper, 1937; Gerard, 1936; Blake and Gerard, 1937) have emphasized the relation of neural excitation level and wave frequency, the two rising and falling together. The present findings with a stimulant, benzedrine, and a depressant, alcohol, fit this picture. On this basis, diminished afferent impulses (perhaps most important, the proprioceptive) playing upon the brain, allow cortical excitation to subside with the gradual loss of consciousness and slowing of potentials. The beta waves retard to 14 per sec. spindles, as Jasper (1937) has shown; and the alpha waves are replaced by, or perhaps are changed into, the slow deltas (Blake and Gerard, 1937). Certainly the appearance of many distinct frequencies within a few minutes, after a prolonged insomnia, suggests that the same cortical neurones can beat at many rates; and the demonstration (Libet and Gerard, 1938 and unpublished) that a few homogeneous cells in the isolated frog olfactory bulb can be made to assume regular rhythms from 1 to 50 per sec. by controlling the excitation level, strongly supports such an interpretation.

It remains uncertain whether the slowed cortical rhythms of sleep are a direct consequence of lowered afferent bombardment or are secondary to a decreased cell metabolism which follows the lowered excitation level. Certainly sensory impulses increase brain heat production (Serota and Gerard, 1938) and, conversely, in sleep brain temperature falls (Serota, 1939). It is also not clear what the role of subcortical centers may be. The fairly simultaneous change in waves over most of the cortex would be in accord with a thalamic or hypothalamic control; and much evidence for such "sleep" centers exists (Hess, 1932; Ranson, 1934; Bard, 1928; Serota, 1939). The cortical changes could, of course, result from a shutting of the thalamic gateway to sensory impulses as well as from a failure to initiate them at peripheral receptors. The excessive somnolence of narcolepsy, associated with pathology in the diencephalon, may well depend on such a "blockade"; that following prolonged insomnia is more probably compounded from both these factors and a direct fatigue depression of cortical neurones as well.

Interpretations of the findings concerned with dreaming is partly beyond the scope of this paper, especially in view of the vast psychiatric literature dealing with the dynamic properties of dreams. We have shown that a subject abruptly awakened, almost at any time during the night, can recall having dreamed; the longer the immediately preceding period with no alpha waves, the less is the recall, and when this period is about a minute (especially if delta waves are present), there is no trace of a dream's having been in progress. This largely excludes the possibility that, in the other states, the dream ran its course as a flash while the subject was actually in the process of waking; presumably dream consciousness, like waking consciousness, blurs and fades progressively as the activity of the cortical neurones falls to lower and lower levels. The conclusion that delta waves appear only in complete unconsciousness, such as coma, narcosis, and epilepsy, as well as dreamless sleep, is forbidden by their presence in drowsing narcoleptics.

Finally, the sequence of changes in passing from wakefulness to deep sleep

and back to wakefulness is of interest. Muscle tone decreases first, then sharp awareness is replaced by dozing or actual dreaming but the subject can still take cognizance of events (dropping a spool, having dreamed), and finally a dreamless oblivion of deep sleep is reached. Disturbances during sleep—external or proprioceptive or perhaps even the building up of excitation in the brain itself—cause a shift towards a lighter state. This is more prolonged when the disturbance occurs late in the night than when it is early and so parallels other signs of asymmetry during a night's sleep. Thus: delta waves appear before the alphas are gone during deepening sleep, but disappear before the alpha waves return during the "null" period; in the descending phase, stimuli convert delta waves to alphas, while in the ascending stage they first initiate delta waves and start alphas only if actually arousing the sleeper; and the alphas just after awakening are feebler than just before going to sleep.

This asymmetry could be accounted for by a combination of two factors. The "fatigued" cortical cells easily fall to a low level of activity when afferent impulses decrease. As they become "rested," sleep lightens even without increased stimulation; and any stimuli that do occur then are relatively more effective than earlier ones.

SUMMARY

1. Minute to minute fluctuations in brain potentials through the night are superimposed on a gradual trend from hour to hour. This latter is compared with the sleep stages described by others. The potentials are present simultaneously over much of the cortex. In sequence, the patterns are: alpha + delta, delta, null, intermittent alpha.

2. During increasing sleep depth, early in the night, delta waves appear before alpha waves are gone; while later, during diminishing depth of sleep, the deltas disappear before the alphas return. In other respects also, potentials of the rising sleep phase do not mirror those of the falling phase.

3. Subjective reports of sleep and dreams can be correlated with potential patterns, sometimes quite sharply.

4. Movement is accompanied by a shift of potentials towards lighter sleep in nine-tenths of the present cases, by no change the remaining times.

5. Hypersomnia, due to prolonged voluntary insomnia or to narcolepsy, is associated with delta waves at relatively higher levels of consciousness than in normal sleep.

6. A stimulant drug, benzedrine, diminishes delta waves; a depressant, alcohol, enhances them.

7. These findings are discussed in relation to theories of sleep and the source of cortical potentials.

* * * *

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HYPOTHALAMIC REGULATION OF BODY TEMPERATURE*

GEORGE CLARK, H. W. MAGOUN, AND S. W. RANSON
Institute of Neurology, Northwestern University Medical School, Chicago

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IT HAS RECENTLY been shown that cats with lesions in the suprachiasmatic region and anterior part of the hypothalamus become overheated when exposed to external temperatures of 102 or 104°F, and that they do not react as readily as normal cats by increased respiratory rate and panting (Teague and Ranson, 1936). In monkeys lesions in the rostral part of the lateral hypothalamus tend to cause a transient hyperthermia while lesions in the caudal part of the lateral hypothalamus cause prolonged hypothermia (Ranson, Fisher and Ingram, 1937). References to other investigations of temperature regulation will be found in the papers listed at the end of this article.

The present paper presents the results of a reinvestigation of the relation of the hypothalamus to temperature regulation. In some cats lesions were placed 1 mm. to the right and left of the midline at the level of the chiasma and in the midline at the level of the infundibulum, causing medially placed damage. In some the lesions were placed at or immediately behind the level of the chiasma and 3 mm. to the right and left of the midline, causing laterally placed damage. In others lesions were placed lateral to the mammillary bodies. In one animal a medially placed lesion destroyed both mammillary bodies. In these animals the lesions were of moderate size. In other experiments huge lesions were made. In some of these the damage was anteriorly placed, in others it was in the middle of the hypothalamus and in still others in its caudal part.

METHODS

The lesions were made with the Horsley-Clarke instrument in the manner previously described (Ingram and Ranson, 1932) except that the two poles of the bipolar electrode were separated by 2 mm. along the long axis of the electrode in order to produce a cylindrical lesion with its long axis corresponding with that of the electrode.

Preceding the operation, daily observations were made of the cat's rectal temperature for a week or more and tests were made of the ability of the animal to regulate its body temperature in the cold box and in the hot box. After the operation the cats were kept for one or more days in an incubator set to run at 86° but varying between 78 and 90°F. Daily observations were made of the rectal and environmental temperature for 2 weeks or more. Tests were made in the hot and cold box about a week after the operation and repeated on the second and fourth weeks and in some cases after much longer intervals. The cold box was the same as that used by Teague and Ranson (1936) and its temperature ranged from 34° to 46° but was usually around 44°F. The hot box was altered by inserting a fan which allowed more even regulation of the temperature within it but because of the increased movement of the air, favored the evaporation of perspiration. The temperature in the hot box was 103 or 104°F. The cats were kept in the box until they panted or until the rectal temperature reached 106°.

* Aided by a grant from the Rockefeller Foundation.

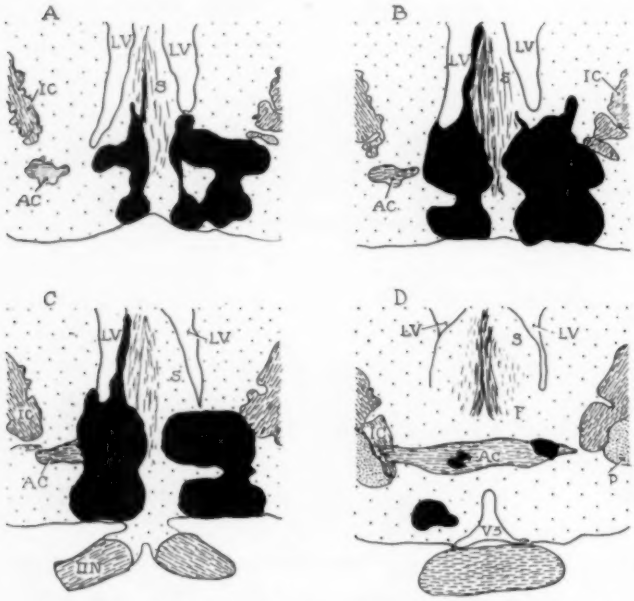

FIG. 1. The lesions in Cat 53 indicated in solid black on four drawings from transverse sections through the brain at the level of and in front of the anterior commissure, lettered in order from before backward.

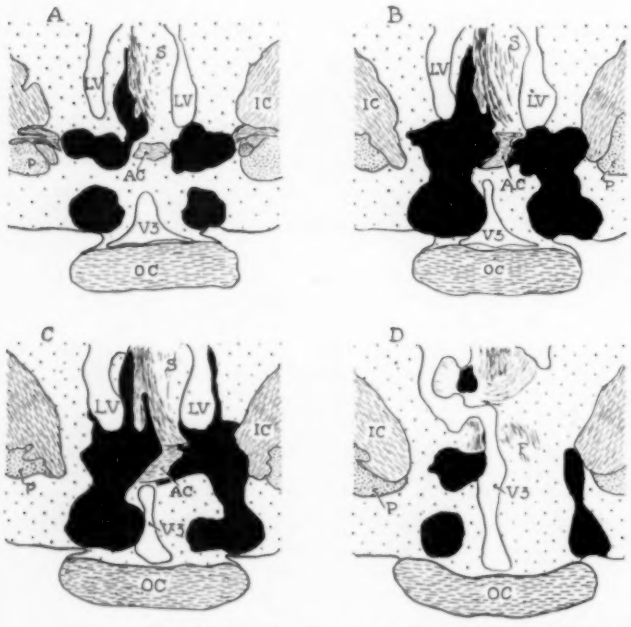

FIG. 2. The lesions in Cat 51 indicated in solid black on four drawings from transverse sections through the brain at the level of and behind the anterior commissure.

ABBREVIATIONS FOR ALL FIGURES

A,BC,D,	Order of sections caudalward
AC	Anterior commissure
CP	Cerebral peduncle
E	Entopeduncular nucleus
F	Fornix
H	Field H of Forel
HG	Habenular ganglion
HP	Habenulopeduncular tract
Hy	Hypophysis
IC	Internal capsule
LV	Lateral ventricle
MLF	Medial longitudinal fasciculus
ME	Median eminence
M	Mammillary body
MP	Mammillary peduncle
MT	Mammillothalamic tract
NII	Optic nerve
NIII	Third nerve
OC	Optic chiasma
OT	Optic tract
P	Globus pallidus
PC	Posterior commissure
S	Septum
Sth	Subthalamic nucleus
SN	Substantia nigra
V3	Third ventricle

Results

In order to form a basis for comparison it was necessary to determine the range of variation in the temperature of normal cats. It can be stated on the basis of 384 observations that the average normal rectal temperature of the cat is 101.4°F. But there is a considerable range of variation so that neither 99.5 nor 102.9° can be considered abnormal. Based on 90 tests, the average rectal temperature at which normal cats begin to pant in the hot box is 103.2° with variations between 105.4 and 101.4°. In the 90 tests, the panting level was above 104.5° in 11, and below 102° in 12. After three hours in the cold box the normal cat's temperature may either have risen or fallen a trifle or if the temperature was high to begin with falls of 1.0 or even 1.5 may occur. A fall of more than 1.0 to a final temperature below 100° is suspicious and any fall below 99.5° is abnormal. Large lesions in the hypothalamus resulted in the death of most of the animals. They would not eat spontaneously and most of them had to be fed by tube as long as they lived. Diarrhea was not uncommon and the nutritive condition poor. The resistance of the animals to infection was low.

Large lesions of the anterior group (Fig. 1 and 2) were less fatal than those situated farther caudally and within this group those situated at the level of or in front of the anterior commissure (A.C. and A.A.C., Table 1) were less fatal than those in the anterior hypothalamus (A.H., Table 1). Of the 20 cats in the anterior group only 8 survived for 1 month or more and only 2 of these were among the 11 with lesions in the anterior hypothalamus. Like all the others these 8 required tube feeding but 6 ultimately ate spontaneously and these were the only ones that survived more than 5 weeks. The night following the operation about half of the animals with anterior lesions defecated excessively, passing large amounts of liquid or soft stools. In these cats insertion of the thermometer for rectal temperature usually caused during the next few days violent defecatory movements and expulsion of the thermometer unless it was firmly held in place. Some of these cats had a diarrhea for several days following the operation. These symptoms were not seen in the two cats with lesions in front of the anterior commissure. Considering their poor physical condition the cats were reasonably alert and showed good motor initiative. None showed catalepsy. One animal showed sham rage and 5 others were extremely surly.

When removed from the incubator on the first morning after the operation the 2 cats with lesions in front of the anterior commissure both had rectal temperatures above 104.5°; 4 of the 7 with lesions at the level of the anterior commissure had temperatures of 104.5° or higher and the lowest temperature in this group was 99°; 3 of the 11 with lesions in the anterior hypothalamus had temperatures above 104.5° and 4 had temperatures below 98°. One of these (Cat 5) continued to run a subnormal temperature and was dead on the fifth day. The temperature of the other 3 was normal or above normal on the second and third days in the incubator. While a majority of the cats of this anterior group ran temperatures which were normal or slightly above on the

Table 1. Postoperative rectal temperatures of cats with very large lesions. The figures in parentheses indicate the temperature of the room or incubator. The cats are listed in three groups according as the lesions are placed in the anterior, middle or posterior parts of the hypothalamus, those of the anterior group are again divided into three divisions designated by the letters A.A.C., cats with lesions anterior to the anterior commissure; A.C., cats with lesions at the level of the anterior commissure; A.H., cats with lesions in the anterior hypothalamus behind the anterior commissure. The cats of the middle group are subdivided into those designated by letter I. with lesions at the level of the infundibulum and those with lesions extending from the level of the infundibulum to the mammillary bodies (I.M.).

Cat	1st Day	3rd Day	5th Day	7th Day	10th Day
Anterior					
A.A.C.					
53	104.6 (85)	104.9 (77)	102.5 (75)	102.6 (75)	102.4 (76)
54	105.6 (85)	103.1 (77)	105.2 (75)	106.0 (75)	Dead
A.C.					
51	99.4 (82)	102.4 (77)	102.0 (75)	98.6 (75)	99.8 (75)
52	105.1 (85)	103.2 (77)	103.7 (75)	103.1 (75)	102.9 (76)
92	105.6 (81)	101.9 (72)	100.4 (73)	101.0 (72)	100.3 (74)
93	99.0 (81)	100.0 (81)	97.7 (81)	<94.0 (81)	Dead
94	104.9 (80)	102.6 (81)	104.4 (81)	99.4 (74)	96.4 (72)
96	104.5 (80)	102.7 (71)	103.3 (73)	101.8 (74)	100.2 (72)
97	100.6 (81)	100.6 (71)	102.0 (72)	100.3 (76)	98.2 (75)
A.H.					
2	98.9 (90)	101.1 (85)	Dead		
5	94.2 (90)	94.9 (84)	Dead		
12	98.3 (84)	97.7 (74)	98.7 (76)	103.6 (76)	97.6 (75)
26	108.5 (89)	98.5 (82)	Dead		
27	105.0 (80)	103.6 (79)	102.9 (77)	102.2 (79)	Dead
79	103.4 (84)	103.6 (75)	100.0 (73)	95.3 (73)	96.9 (74)
80	104.1 (81)	98.3 (71)	94.9 (73)	Dead	
81	105.3 (81)	103.2 (71)	99.2 (73)	99.6 (73)	100.6 (72)
82	95.8 (84)	101.5 (80)	94.0 (73)	94.4 (75)	92.7 (72)
83	94.3 (80)	104.2 (80)	101.4 (75)	96.3 (72)	98.2 (73)
85	96.9 (84)	107.9 (73)	105.9 (74)	Dead	
Middle I.					
32	94.4 (84)	92.0 (83)	92.2 (84)	98.4 (88)	Dead
33	96.2 (82)	92.3 (77)	100.8 (85)	93.5 (75)	Dead
34	96.4 (86)	96.8 (85)	93.3 (75)	95.8 (84)	Dead
36	99.1 (88)	99.8 (74)	102.3 (75)	101.1 (75)	Dead
37	102.4 (88)	96.3 (74)	95.3 (75)	Dead	
I.M.					
31	96.6 (79)	93.6 (82)	99.5 (86)	98.4 (75)	100.3 (77)
35	100.3 (86)	93.1 (85)	101.3 (75)	94.4 (75)	Dead
Posterior					
28	95.2 (85)	96.6 (84)	103.1 (84)	100.0 (84)	Dead
71	92.5 (83)	103.4 (83)	Dead		
72	94.4 (83)	Dead			
73	93.4 (84)	100.9 (82)	Dead		
74	<92.0 (84)	98.2 (82)	Dead		

second and third days some of these developed subnormal temperatures before the tenth day (Table 1). It is important to note that the incidence of subnormal temperatures increased with the lapse of time following operation, which is just the opposite of what is seen after lesions farther back in the hypothalamus. Cat 97, whose temperature was normal for the first 5 days and varied from normal to slightly subnormal during the next 15 days, was found on the 60th day, following an interval in which no temperatures were recorded, to have a rectal temperature of 97°. During the next 9 days its temperature did not rise above 98°. It was below 97° on 6 of the 9 days and once reached 94.1°. This animal was in excellent physical condition and had a good appetite and a sleek coat of hair.

Because of the early death or poor condition of a majority of these cats only 7 were tested in the cold box and 8 in the hot box. Three of the 7 showed abnormal reactions in the cold box, their rectal temperature dropping to 92.4, 95 and 95.4° respectively. Two of these 3 shivered and in the third shivering was questionable (Table 2).

Table 2. Cold box tests on cats with large anteriorly placed lesions. Rectal temperature in degrees Fahrenheit

Cat no.	Days after operation	Level of lesion	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box
53	14	A.A.C.	102.0	101.9	−0.1	?	49
51	15	A.C.	103.1	102.7	−0.4	?	49
94	18	A.C.	98.0	95.4	−2.6	yes	42
96	79	A.C	99.1	95.0	−4.1	?	44
97	74	A.C.	98.0	92.4	−5.6	yes?	44
12	104	A.H.	101.2	101.0	−0.2	?	39
81	73	A.H.	103.6	101.6	−2.0	yes	39.5

Hot box tests showed that in this group of animals there was a marked loss in ability to regulate against heat (Table 3). In all but one cat the rectal temperature rose above 106° without causing panting or much increase in respiratory rate. In 6 of the cats the rate did not exceed 36 per minute. One cat (53) panted at a rectal temperature of 104.5° and it is interesting to note that this was the only one in which the lesions were situated so far forward as to spare most of the anterior commissure and much of the preoptic region (Fig. 1). In Cat 51 the lesions involved the anterior commissure and the brain ventral to it thus largely destroying the preoptic region (Fig. 2). In the hot box test made on this cat 38 days after the operation the rectal temperature reached 106.4° without causing panting or an increase in respiratory rate above 72 (Table 3). The difference between the reactions of these two cats in the hot box, the one with the preoptic region largely intact showing a normal reaction and the one with this region largely destroyed showing a failure to pant, fits very well with the results obtained by Magoun, Harrison, Brobeck and Ranson (1938) by local heating of the brain. The anterior limits of the area concerned with heat loss activity as determined by heating the brain

coincide within half a millimeter with the limits of this area as determined by lesions.

Large lesions of the middle group, destroying most of the hypothalamus from the chiasma to the caudal border of the attachment of the hypophyseal stalk (I., Table 1) and in two cases involving also the level of the mammillary bodies (I.M., Table 1), were invariably fatal. The period of survival of the 7 cats of this group varied from 5 to 11 days, the average being 8 days. None of the cats ate spontaneously. Two (31 and 35) with lesions extending far enough back to involve the level of the mammillary bodies were drowsy, cataleptic and lacking in motor initiative on the day following the operation, four of

Table 3. Hot box tests on cats with large anteriorly placed lesions. Rectal temperature in degrees Fahrenheit

Cat no.	Days after operation	Level of lesion	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating
53	35	A.A.C.	104.5	3.6	140	yes	yes
51	38	A.C.	106.4	4.3	72	no	not tested
94	30	A.C.	106.2	13.8	16	no	no
96	81	A.C.	106.4	8.3	22	no	no
97	64	A.C.	106.2	7.8	24	no	not noticed
12	104	A.H.	106.3	4.3	36	no	no
81	71	A.H.	106.0	3.2	24	no	no
83	28	A.H.	106.2	5.6	32	no	no

the others were alert and active and the remaining one slightly less active. Only one of the cats defecated excessively. Two others made violent movements of defecation when the thermometer was inserted and another pair developed a marked diarrhea. Not one was excessively irritable. None of these cats shivered spontaneously. On several occasions one (32) was observed panting in the incubator, although it was running a rectal temperature of 94° or less. These cats ran for the most part subnormal temperatures although in three (35, 36, 37) the temperature was normal on the morning after the operation when the cat was removed from the incubator.

Hot box tests were made on 6 cats of this group. Five of them failed to pant before their rectal temperature reached 106°. The other cat (32), however, panted at 103.7°. This was the cat which on several occasions was observed panting in the incubator with a rectal temperature of about 94°. No cold box tests were made in this group.

Large lesions destroying the posterior part of the hypothalamus were made in 5 cats. None of these animals lived more than 7 days and the brains were not prepared for microscopical study; but free hand sections indicated practically complete destruction of the hypothalamus at the level of the mammillary bodies. The first morning after the operation the animals seemed asleep, the eyes were closed and they could not stand. Three were limp with no tone in the postural muscles. Two showed some tonicity on the first day but were

flaccid the next day. As long as they lived these animals were absolutely quiet, remaining where and as they were placed. Due to the lack of muscular tonus they could not be posed in any position requiring muscular effort. None of these animals ever ate spontaneously and all required tube feeding. Two developed diarrhea. On the morning after the operation the highest temperature recorded was 95.2° and the lowest was below 92, Table 1. These cats ran subnormal temperatures in the incubator as long as they lived, except cats 28 and 73 which recorded 100° and 100.9° the day before they died and

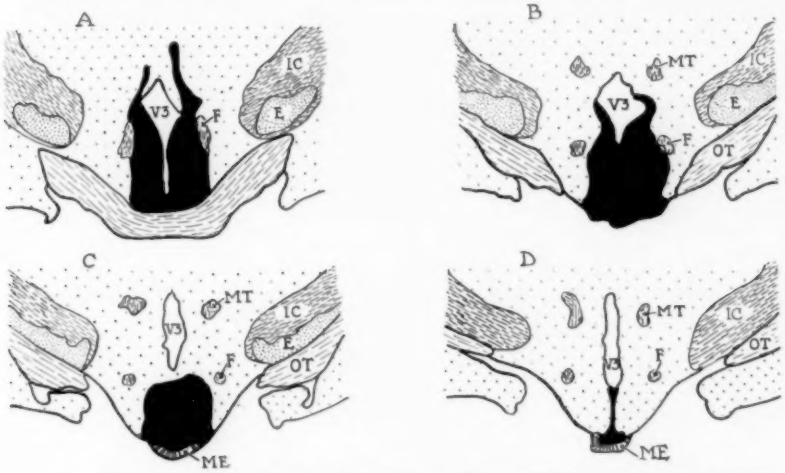

FIG. 3. The lesions in Cat 13 indicated in solid black on four drawings from transverse sections through the brain at the level of and behind the optic chiasma.

Cat 71 which had temperatures of 101.4 and 103.4 on the second and third days. On autopsy the lungs were found congested or consolidated in each case. No hot or cold box tests were made on these animals.

Moderate sized lesions offer much more information about functional localization than do the massive lesions considered in the preceding section. These smaller lesions have been so placed as to destroy selectively rostromedial, rostrolateral, caudomedial or caudolateral portions of the hypothalamus.

Small or moderate sized lesions in the medial part of the anterior hypothalamus in 17 cats produced no easily recognizable symptoms. On the morning after the operation these animals were alert and active. They usually ate spontaneously on the first or second postoperative day and none of them showed a postoperative diarrhea. Their daily temperatures subsequent to the operation were normal except that a considerable number of them had temperatures in the range of 104 or 105° on the first postoperative day. Eight of these cats on which hot and cold box tests were made are listed in Tables 4, 5 and 6. Their reactions in the cold box were entirely normal. In the hot box tests made one month after the operation their records were only slightly abnormal as shown by comparison with the similar preoperative tests recorded in the

same table. There was some elevation of the panting temperature level and decrease in final respiratory rate as judged by the preoperative controls; but they all panted at rectal temperatures below 106.°

The lesions lay close to the midline and in Cat 13 extended from the optic

Table 4. Postoperative rectal temperatures in degrees Fahrenheit of cats with moderate sized hypothalamic lesions. The figures in parentheses indicate the temperature of the room or incubator. The cats are listed in four groups: those with anteromedial lesions are designated by the letters AM; those with anterolateral lesions, AL; those with posteromedial lesions, PM; and those with posterolateral lesions, PL.

Cat	1st Day	3rd Day	5th Day	7th Day	10th Day
A.M.					
6	103.2 (84)	101.7 (75)	102.0 (75)	101.2 (77)	101.0 (77)
11	105.0 (84)	103.0 (75)	103.3 (76)	101.9 (76)	103.0 (75)
13	102.6 (84)	102.5 (76)	103.0 (76)	102.3 (75)	103.2 (75)
15	103.0 (87)	103.2 (76)	104.0 (75)	103.8 (75)	
16	105.4 (87)	104.9 (76)	102.9 (75)	103.3 (75)	
17	103.5 (87)	103.6 (75)	104.1 (75)	D.C.	
18	104.6 (87)	102.0 (75)	101.8 (75)	D.C.	
22	104.4 (82)	102.2 (74)	101.3 (75)	101.9 (74)	101.6 (73)
A.L.					
8	107.9 (84)	103.7 (76)	103.5 (77)	102.1 (74)	101.8 (76)
20	94.0 (78)	102.1 (85)	101.0 (76)	99.3 (76)	100.7 (75)
40	104.6 (82)	106.0 (74)	98.2 (74)	104.9 (72)	100.1 (74)
23	104.6 (85)	104.7 (76)	103.6 (76)	103.2 (75)	102.5 (75)
39	102.1 (82)	101.9 (74)	102.7 (74)	102.0 (72)	100.7 (74)
42	105.1 (85)	103.8 (76)	102.7 (76)	101.3 (75)	102.5 (75)
43	105.2 (82)	99.6 (74)	98.7 (74)	97.3 (72)	101.3 (74)
55	106.0 (82)	100.1 (76)	101.7 (76)	102.4 (76)	
P.M.					
103	102.1 (86)	103.6 (76)	102.1 (76)	102.2 (76)	103.3 (74)
25	101.6 (81)	104.0 (77)	103.2 (75)	101.2 (75)	101.4 (75)
38	101.8 (81)	103.5 (77)	103.5 (75)	103.8 (75)	103.5 (75)
105	97.1 (84)	103.1 (77)	103.8 (77)	102.5 (77)	103.2 (77)
P.L.					
46	90.6 (83)	102.9 (82)	97.6 (74)	99.6 (74)	99.3 (77)
47	87.0 (83)	105.4 (82)	97.6 (74)	102.6 (74)	103.7 (77)
100	91.0 (82)	100.2 (?)	98.8 (77)	105.7 (79)	102.6 (77)
107	94.7 (82)	97.1 (79)	103.6 (77)	102.9 (75)	102.5 (75)
109	93.4 (88)	99.1 (90)	101.8 (91)	96.4 (73)	98.2 (74)
110	95.6 (84)	99.4 (86)	99.5 (84)	99.5 (76)	101.1 (74)
114	96.0 (85)	98.6 (84)	99.9 (73)	102.3 (75)	101.4 (77)

chiasma to the fornix and caudalward over the median eminence (the expanded end of the infundibulum where this is attached to the tuber) as shown in Fig. 3. In this cat the daily temperature remained within normal limits (Table 4). In some of the others temperatures of 104 and 105° were encountered. The important thing is that at no time did any of these cats show a loss in capacity to keep the body temperature up to the normal level. Five days after the

operation Cat 13 was in the cold box for 3 hours at a temperature of 42° without any significant drop in its rectal temperature (Table 5).

When tested in the hot box one month after the operation Cat 13 panted at a rate of 132 per min. at a rectal temperature of 104.1 as compared with a respiratory rate of 230 per min. and a temperature of 101.7° in the preoperative test (Table 6). In hot box tests made one week after the operation two of these cats with medial lesions failed to pant at temperatures below 106°. Of these two, one had a respiratory rate of 78 at 106.1° and the other, a rate of 212 at 106.2°. At the end of a month, however, both of these cats (11 and 22) had merely an increase in panting level of about 1.5° above the preoperative level (Table 6). The cats in this group showed somewhat less disturbances in regulation against heat than did those reported by Teague and Ranson (1936) and this is to be correlated with the fact that the lesions did not extend quite as far lateralward (Fig. 3). All of the cats of this group

Table 5. Cold box tests on cats with medial lesions in the rostral part of the hypothalamus. Rectal temperature in degrees Fahrenheit.

	Preoperative tests					Tests made during the first postoperative week				
Cat no.	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box
6	100.8	100.8	0	yes	41	102.5	102.1	−0.4	yes	44
11	101.8	101.9	+0.1	yes	46	103.3	103.8	+0.5	yes	44
13	101.7	101.2	−0.5	yes	45	101.6	101.0	−0.6	yes?	42
15	101.3	101.0	−0.3	yes	45	102.4	102.1	−0.3	yes	42
16	101.3	99.6	−1.7	yes	43	104.5	103.6	−0.9	yes	42
17	102.5	101.1	−1.4	yes	46	102.9	102.1	−0.8	yes	43
18	101.7	101.7	0	yes	43	101.5	101.2	−0.3	yes	43
22	101.0	99.5	−1.5	yes	44	101.8	100.0	−1.8	yes	45

reacted normally in the cold box tests made during the first postoperative week (Table 5).

Moderate sized lesions in the lateral part of the anterior hypothalamus caused much greater disturbance in temperature regulation than did those more medially placed. There were 8 cats in this series and of these, 3 (8, 20, 40) had symmetrically placed lesions in the extreme lateral part of the hypothalamus, reaching and often damaging the medial edge of the basis pedunculi and internal capsule (Fig. 4). The region, between the fornix and internal capsule above the optic chiasma, which contains the medial forebrain bundle was destroyed on both sides of the brain. The remaining 5 cats had lesions asymmetrically placed so that a considerable part of the medial forebrain bundle escaped damage on one or the other sides.

On the morning after the operation all 8 of these animals were alert and active. Some of them had multiple soft stools during the night following the operation. Two of the three cats with symmetrical lesions did not eat spontaneously after the operation but required tube feeding for the rest of their

lives. The other cats required tube feeding for a time which averaged about 11 days. In all but one case the rectal temperature was normal or above normal on the morning following the operation. The exception, Cat 20, had a subnormal temperature on the first postoperative morning but on the second and third days it was normal (Table 4). Six cats on the morning following the operation had temperature above 104.5 and in one it reached 107.9°. The

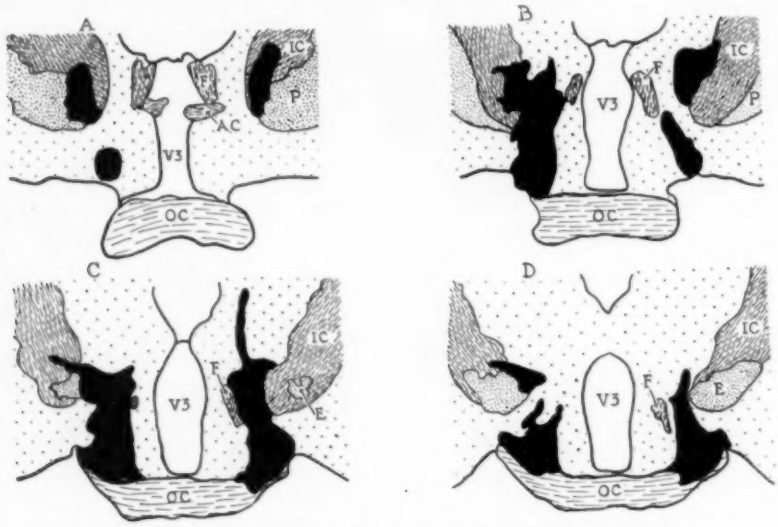

FIG. 4. The lesions in Cat 8 indicated in solid black on four drawings from transverse sections through the brain at the level of the optic chiasma.

second day three had temperatures above 104.5. Soon thereafter all temperatures became normal and remained so except for Cat 20 which for 23 days (from the 22nd to the 45th postoperative day) ran a subnormal temperature as low as 97°F.

Table 6. Hot box tests on cats with medial lesions in the rostral part of the hypothalamus. Rectal temperature in degrees Fahrenheit.

	Preoperative tests					Tests one month postoperative				
Cat no.	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating
6	102.7	0.3	184	yes	no	103.0	2.2	146	yes	no
11	104.1	2.4	112	yes		105.7	4.2	186	yes	yes
13	101.7	0.9	230	yes	no	104.1	2.9	132	yes	no
15	103.0	0.5	160	yes	yes	105.9	3.5	126	yes	no
16	105.2	2.5	224	yes	no	104.1	2.0	196	yes	yes
17	102.1	0.8	216	yes	yes	105.3	4.0	180	yes	no
18	103.9	0.9	184	yes	yes	105.0	2.2	180	yes	no?
22	102.8	0.4	260	yes	no	104.3	3.8	216	yes	yes

The three cats with symmetrical lesions (8, 20, 40) suffered a marked loss in ability to prevent overheating as measured by the respiratory responses to hot box tests one month after the operation (Table 7). In each of these the rectal temperature was raised to 106° without causing panting and without causing much increase in the respiratory rate. Later tests (Cat 40, 6 weeks; Cat 20, 10 weeks and Cat 8, 16 weeks) revealed little improvement in ability to resist overheating except that Cat 8 showed some increase in respiratory rate. However, 27 weeks after the operation Cat 8 was able to pant at 105.3°, thus showing a delayed and partial recovery of the capacity to regulate against heat.

The cats with asymmetrical lateral lesions showed an early loss in the ability to regulate against heat. In tests made one week after the operation Cats

Table 7. Hot box tests on cats with lateral lesions in the rostral part of the hypothalamus. Cats 8, 20 and 40 had symmetrical lesions, the other four had asymmetrical lesions. Rectal temperature in degrees Fahrenheit.

	Preoperative tests					Tests one month postoperative				
Cat no.	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating
Sym.										
8	104.5	3.2	176	yes	no	106.2	3.8	70	no	yes
20	104.4	2.3	230	yes	yes	106.0	7.7	26	no	no
40	103.3	1.3	246	yes	yes	106.0	2.8	36	no	no
Asym.										
23	103.1	−0.2	206	yes	yes	103.9	2.6	220	yes	yes
39	102.7	0.4	252	yes	yes	105.9	3.7	140	yes	no
42	104.0	1.4	176	yes	yes	104.9	3.8	120	yes	yes
43	102.7	0.6	240	yes	yes	105.9	2.6	222	yes	no

39 and 43 reached temperatures above 106° without panting and with almost the same respiratory rates as at the beginning of the tests. The other two (23 and 42) did not pant at this temperature although the respiratory rate was high. However, one month after the operation Cats 23 and 42 had so far recovered that the panting levels were less than 1° above the preoperative levels and Cats 39 and 43 panted at 105.9°. Cold box tests on the cats with symmetrical lesions showed greater than normal drops in temperature, though in the tests made one month after the operation the final temperatures reached were not abnormally low. The cats with asymmetrical lesions gave normal reactions in the cold box (Table 8).

It is evident from the data presented that symmetrical lesions in the lateral part of the rostral hypothalamus are much more effective than asymmetrical lesions in causing disturbances in temperature regulation but even symmetrical lesions do not cause great loss in the capacity to regulate against cold. But such symmetrical lateral lesions cause a profound and prolonged loss in the ability to regulate against heat.

Laterally placed moderate sized lesions in the posterior part of the hypothalamus cause very great impairment in the ability to regulate against both heat and cold. The seven cats in this series had lesions at the level of the mammillary bodies extensively damaging the lateral hypothalamic area. In all but

Table 8. Cold box tests on cats with lateral lesions in the rostral part of the hypothalamus. Cats 8, 20 and 40 had symmetrical lesions. The other four had asymmetrical lesions. Rectal temperature in degrees Fahrenheit.

	Tests one week postoperative					Tests one month postoperative				
Cat no.	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box
Sym.										
8	102.6	97.4	−5.2	yes	40	103.0	100.6	−2.4	yes	39
20	99.5	97.1	−2.4	yes?	44	102.1	99.6	−2.5	yes?	42
40						102.7	99.7	−3.0	no	43
Asym.										
23	101.7	100.4	−1.3	yes?	45	102.4	101.8	−0.6	yes?	39
39						102.1	101.8	−0.3	yes?	43
42	103.2	102.4	−0.8	yes?	44	101.8	102.4	+0.6	yes?	40
43						101.9	102.0	+0.1	yes	44

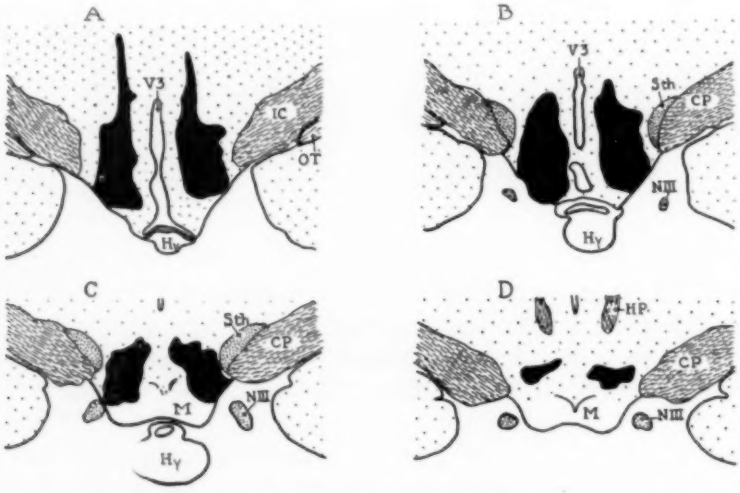

FIG. 5. The lesions in Cat 47 indicated in solid black on four drawings from transverse sections through the brain at the level of and in front of the mammillary body.

one the lesions were fairly symmetrical bilaterally and in most instances they extended far enough dorsally to involve the fields of Forel and to interrupt any fibers which may run through the supramammillary decussation from the lateral hypothalamic area to the central gray matter. In Cat 47 (Fig. 5) the lesions were situated somewhat farther rostrally than in the others and extended from the level of the infundibulum to the level of the middle of the

mammillary bodies. In Cat 110 the lesions were placed farther caudally (Fig. 6). In one cat (114) the lesions were quite asymmetrical one being in the lateral hypothalamic area on the left side, the other being in the midline leaving the right lateral hypothalamic area largely intact. These lesions would have interrupted in addition to the fibers descending on the left side into the mesencephalic tegmentum any fibers which may enter the central gray matter through the supramammillary decussation. This cat showed marked disturbances in temperature regulation, a month after the operation but tests were not made after 2 or 3 months to determine to what extent recovery may have taken place.

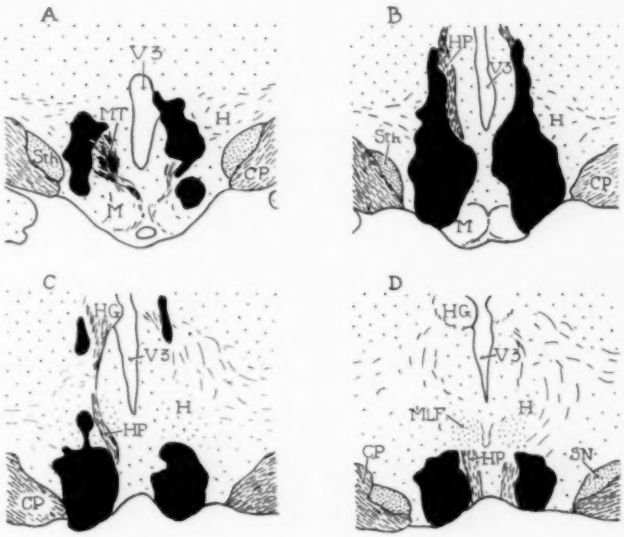

FIG. 6. The lesions in Cat 110 indicated in solid black on four drawings from transverse sections through the brain at the level of and behind the mammillary bodies.

On the morning after the operation these animals were lethargic. There was considerable extensor tonus especially in the hind legs and the cats could be molded into various bizarre postures similar to those assumed by the cataleptic cats previously described (Ingram, Barris and Ranson, 1930). Usually within 4 days after the operation the catalepsy disappeared and the cats became alert and active and would eat spontaneously. There was no postoperative diarrhea such as occurred in many of the animals with lesions situated farther forward. On the morning after the operation they had, when removed from the incubator, rectal temperatures of 96° or less (Table 4). On the seventh day they all were able to maintain normal temperatures in the warm animal room except Cat 109.

In cold box tests all of these cats showed a marked decrease in ability to prevent a loss of body heat (Table 9). Five of the 7 showed in one or more of the tests drops of more than 7° as a result of 3 hours exposure to temperatures ranging from 34 to 44°. In 2 (Cats 100, 107) there was evidence of partial recovery of ability to keep warm with the lapse of time. But in the others practically no recovery occurred within the limits of time intervening between the first and last tests. Cat 47 showed a drop of 9.7°, 123 days after the operation; Cat 109 showed a drop of 7.8°, 68 days after the operation; and in Cat 110 the temperature dropped 3.5 to 96.6° in the test made 62 days after the operation. It will be obvious, therefore, that while most of the cats ran an

approximately normal temperature when kept in a warm room a week after operation, this cannot be regarded as evidence for a return of normal temperature regulation.

The postoperative hot box tests showed a marked loss in ability to regulate against overheating (Table 10). With rectal temperatures of 106° none of the cats panted and the respiratory rate remained slow. The information at hand does not necessarily show that the ability to pant was abolished by

Table 9. Cold box tests in cats with lateral lesions in the caudal part of the hypothalamus. Rectal temperature in degrees Fahrenheit.

Preoperative tests						Postoperative tests					
Cat no.	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box	Days after operation	Temp. at start	Temp. at end	Change	Shivering	Av. temp. of box
46	102.3	99.7	−2.6	yes	44	6	100.3	96.9	−3.4	yes	42
						41	100.4	97.0	−3.4	yes	40
47	101.3	100.0	−1.3	yes	44	18	102.6	93.6	−9.0	no?	44
						123	102.6	92.9	−9.7	no?	39
100	101.5	101.8	+0.3	yes	46	20	102.3	94.6	−7.7	yes	41
						55	102.6	98.4	−4.2	yes?	40
107	101.8	102.1	+0.3	yes	41	26	103.8	96.2	−7.6	no	37
						84	102.8	100.0	−2.8	no	35
109	101.9	101.7	−0.2	no	42	33	102.3	98.0	−4.3	no	37
						68	102.5	94.7	−7.8	no	36
110	101.1	100.3	−0.8	yes	36	32	101.0	96.7	−4.3	no	41
						62	100.1	96.6	−3.5	no	36
114	101.7	101.0	−0.7	no?	34	33	102.7	94.6	−8.1	no	34

these lesions. Certainly the threshold for panting was raised above 106°, but in those cats in which the rectal temperature was forced sufficiently high, panting occurred. In a test made on Cat 46, 49 days after the operation, the box temperature was raised to 114° and panting began when the rectal temperature reached 109.7°. This test was made long after the operation and it is possible or even probable that had a similar effort been made to force panting within a week or so after the operation the animal's temperature would have reached a fatal level before panting occurred.

Medially placed moderate sized lesions in the caudal part of the hypothalamus. caused little disturbance in temperature regulation. There were 3 cats with unilateral lesions destroying one mammillary body and one cat (103) with bilateral lesions destroying both mammillary bodies. The temperatures of all these cats during the postoperative days were normal except that one cat (105) with a unilateral lesion had a subnormal temperature on the first post-

operative morning. Hot and cold box tests made from 2 to 4 weeks after the operation were normal. Earlier tests were not made in any of these cats except in one (Cat 25) with unilateral destruction of the mammillary body. On the second postoperative day this cat failed to pant in the hot box although its respiration was 156 when its temperature reached 106°. In a later test this cat reacted normally in the hot box and the poor performance on the second day is to be explained by a transient impairment of function in regions outside the anatomical lesion.

The chief interest lies in Cat 103 with bilateral destruction of the medial part of the caudal hypothalamus (Fig. 7). The lesions destroyed all of both mammillary bodies except the rostral tip of the one on the right and every thing dorsal to the mammillary bodies as far as the floor of the

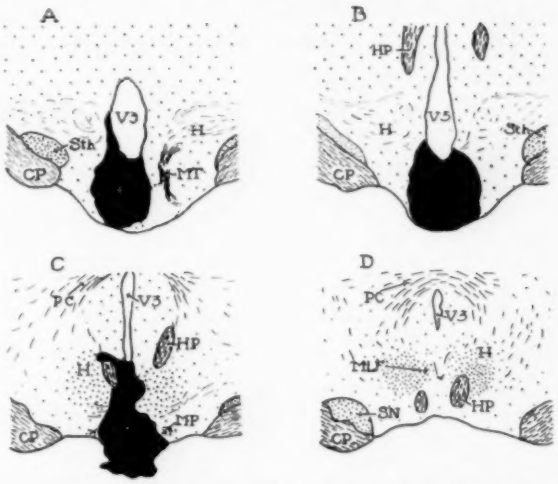

FIG. 7. The lesions in Cat 103 indicated in solid black on four transverse sections through the brain at the level of and behind the mammillary bodies.

Table 10. Hot box tests on cats with lateral lesions in the caudal part of the hypothalamus. Rectal temperature in degrees Fahrenheit.

	Preoperative tests						Postoperative tests				
Cat no.	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating	Days after operation	Temp. at end of test	Rise in temp.	Final respiratory rate	Panting	Sweating
46	105.1	2.1	208	yes	no	7	106.2	8.4	42	no	no
						20	106.0	7.5	30	no	no
47	103.4	1.6	300	yes	no	7	106.0	3.2	26	no	no
						42	106.0	3.0	28	no	no
100	102.0	−0.1	240	yes	yes	28	106.1	3.5	66	no	no
107	103.3	1.1	230	yes	no	26	106.3	6.2	30	no	no
						42	106.3	3.4	40	no	no
109	103.4	1.1	180	yes	no	33	106.0	5.4	20	no	no
						66	106.0	4.1	36	no	no
110	101.8	0.9	210	yes	yes	32	106.3	3.9	30	no	no
						56	106.0	4.4	30	no	no
114	102.5	0.9	240	yes	yes	35	106.0	1.9	140	no	no

third ventricle. In this cat the lesion was in a position to interrupt fibers which descend from the hypothalamus through the central gray matter of the aqueduct; but the main pathway which runs lateral and dorsolateral to the mammillary body was intact on both sides. This cat showed no disturbance in temperature regulation so far as could be determined by the daily temperature records and by the hot and cold box tests made 30 days after the operation. It is quite possible that had these tests been made within a day or two after the operation transient abnormalities would have been detected.

Discussion

It is difficult to make accurate observations on sweating and shivering. Sweating, which in the cat occurs only on the pads of the feet and is never profuse, is often obscured by evaporation. In the preoperative tests shown in Table 10 only 3 of the cats were observed to sweat and 4 were not. Hence no great importance can be attached to the fact that in the postoperative tests shown in the same table none of the cats were observed to sweat. It is not always easy to tell whether or not a cat is shivering. In the postoperative tests shown in Table 9, Cat 47 showed some twitching of the muscles which did not feel to the observer's hand like shivering and the observation was entered as a questionable negative. Shivering was not always detected in the preoperative tests. Two of the cats with lateral lesions in the caudal part of the hypothalamus did shiver during the postoperative tests. Hence it is not possible to say that these lesions abolished shivering although shivering occurred less often in the operated than in the unoperated cats.

The *delayed hypothermia* which developed after the lapse of from 7 to 10 days as a result of large anteriorly placed lesions (Table 1) in cats which had had normal or higher than normal rectal temperatures during the first postoperative days is difficult to explain. It differs from the hypothermia caused by more posteriorly placed lesions in that the latter appears promptly after the operation and decreases with the lapse of time. The explanation for this delayed hypothermia may perhaps in some instances lie in a toxic depresson of the rest of the hypothalamus due to the diffusion of substances formed in the lesions.

It does not seem probable that the explanation could lie in the malnutrition resulting from the refusal of the animals to eat. To test this possibility, normal cats have been deprived of food for many days and it was found that their capacity to regulate against cold was not impaired until they had lost 30 per cent or more of their body weight (Clark, 1938). Few of the cats with preoptic lesions were as emaciated as this since they all received 100 cc. of milk daily by stomach tube. One of the cats (no. 97) had a rectal temperature of 97°, 60 days after the operation although at this time it was eating well and was in good physical condition. Incidentally the existence of hypothermia in this animal 60 days after the operation also speaks against the theory of a toxic depression of the hypothalamus in so far as the debris from the preoptic lesions would have been absorbed by this time. It must be admitted that no satisfactory explanation for this delayed hypothermia is available at present.

Increased peristaltic activity of the intestines, as evidenced by the passage of large amounts of soft stools during the night following the operation, diarrhea, and violent defecatory movements induced by the insertion of the thermometer was seen in a considerable number of the animals especially in those with large anteriorly placed lesions. If this were due entirely to elimination of sympathetic inhibitory tonus emanating from the hypothalamus it should have appeared more frequently in the animals with lesions in the middle and posterior parts of the hypothalamus. This would seem to indicate that stimulation of the gut is involved but no information is furnished about the source of such stimulation.

Diarrhea frequently develops in cats with hypothalamic lesions when because of their refusal to eat spontaneously they are subjected to tube feeding with 100 cc. of milk daily. Normal cats when deprived of all food except 100 cc. of milk daily do not develop a diarrhea whether they drink the milk or have it given them by tube. The milk diet may cause them to have soft stools but not a diarrhea.

Chilling. Little if any information concerning the localization of heat regulating centers can be obtained from the experiments in which very large lesions were made. The smaller lesions are much more instructive. Subnormal temperatures were observed on the first postoperative morning in none of the cats with medially placed lesions and in only one of the cats with laterally placed lesions in the anterior hypothalamus (Cat 20, Table 4). The cats with moderate sized laterally placed lesions in the posterior part of the hypothalamus showed a marked hypothermia the first morning after the operation, but there was a rather rapid recovery so that on the 10th day only two of them had temperatures below 101° (Table 4). It would appear that cats recover from the hypothermia caused by hypothalamic lesions more rapidly than do monkeys; but even monkeys regain the ability to maintain normal body temperatures under ordinary room conditions in a few weeks (Ranson, Fisher and Ingram, 1937).

But rectal temperatures of animals kept under ordinary room conditions do not furnish a satisfactory measure for their ability to regulate against cold. For this purpose cold box tests are required. Such tests made during the first postoperative week gave normal results in cats with medially placed anterior lesions (Table 5) and abnormally large drops in cats with symmetrical lateral lesions in the anterior part of the hypothalamus. Even after one month these cats with symmetrical anterolateral lesions still showed falls in temperature which were considerably greater than normal (Table 8). By far the greatest chilling, however, was seen in the cold box tests on cats with laterally placed lesions in the posterior part of the hypothalamus (Table 9).

It is particularly significant that these cats with posterolateral lesions showed little tendency to recover the ability to prevent chilling in the cold box, the temperature of Cat 47 falling 9.7° in three hours in a box at 39° in a test made 123 days after the operation. In 2 of the cats listed in Table 9 there was evidence of some recovery. But in one of these (Cat 100) the lesions were somewhat asymmetrical and in the other cat (107) the lesions were much

smaller than in the other cats of this group. The recovery of ability to resist chilling in the cold box shown by these cats was evidently due in large part to the incompleteness of the lesions.

Considerable difference of opinion exists with regard to the extent to which subsidiary centers are capable of contributing to temperature regulation in the absence of the hypothalamus. Keller (1933) and Thauer and Peters (1937) found recovery of ability to maintain a normal body temperature under ordinary environmental conditions in chronic midbrain animals, though a normal regulation against extremes of external temperature was never regained. The perfect protection against cold offered by the fur of the rabbit may in part account for Thauer's (1935) finding that some time after the transection of the cervical cord that animal was able to preserve body temperature in a fairly normal manner, for his results are not in accord with those of Sherrington on the dog (1924) or Clark (1939) on the cat.

Overheating. Hyperthermia was present in many of the cats on the morning after the operation. In the group with large anterior lesions 9 out of 20 cats had temperatures above 104.2°. Four out of 8 cats with medially placed moderate sized lesions in the anterior hypothalamus and 6 out of 8 cats with laterally placed moderate sized lesions in the anterior hypothalamus also had temperatures above 104.2 on this first morning. These high temperatures can scarcely be attributed to nonspecific results of the operation, because in a group of cats in which similar lesions were made in the thalamus by the same method the temperatures on the first postoperative morning were 102.1, 102.3, 103.6, 103.7 and 104.1° respectively. In these as in all the cats with hypothalamic lesions the rectal temperatures were taken on the first morning at the time the cats were removed from the incubator in which they had been kept over night so that the factor of environmental temperature was essentially the same in all cases. Under these conditions normal cats regulated their temperatures perfectly and many of the cats with hypothalamic lesions showed subnormal temperatures. The hyperthermia seen in some of the cats cannot, therefore, be attributed to the high temperature of the incubator.

The location of the lesions in the animals with high temperatures on the first postoperative morning have varied a good deal. Large lesions in front of the anterior commissure (Cats 53 and 54), at the level of the anterior commissure (Cats 52 and 92) or in the suprachiasmatic hypothalamus (Cats 27 and 81) and smaller lesions either medially placed at the level of the infundibulum (Cats 11 and 18) or in the anterior part of the lateral hypothalamus (Cats 8 and 42) have frequently caused hyperthermia. It would seem most reasonable to attribute the rise in temperature to an irritation of the mechanism for heat conservation and heat production since in none of these animals was most of the hypothalamus destroyed and the most distant lesions were within 2 mm. of it. Many of these cats showed impaired capacity to regulate against heat as measured by the hot box tests, and this probably was a factor in permitting the high temperatures to develop. But this factor is not in itself sufficient to cause hyperthermia. In Cats 8, 20 and 40 the impairment of capacity to prevent overheating persisted for at least a month but

hyperthermia lasted for only a few days in 8 and 40 and did not appear in 20.

The capacity to regulate against overheating as measured by the hot box test was very seriously disturbed in all but one of the cats with large anteriorly placed lesions which were subjected to this test. It is significant that in all but this one the region dorsal to the optic chiasma was extensively damaged. A month or more after the operation these cats failed to pant or to show much of an increase in respiratory rate when their temperatures were raised to 106° or higher (Table 3). The exception was Cat 53 in which the lesions were situated in front of the anterior commissure and a large part of the preoptic region remained intact. Cats from which the frontal lobes had been removed for another purpose (Magoun and Ranson, 1938) also showed normal reactions in the hot box.

Cats with smaller medially placed lesions in the anterior part of the hypothalamus showed after one month only a moderate increase in the panting level and in respiratory rate (Table 6). But cats with moderate sized symmetrical lesions in the lateral part of the anterior hyopthalamus failed to pant and showed little increase in respiratory rate when their rectal temperatures had been raised to 106° one month after the operation (Table 7, Fig. 4). All of the cats with laterally placed lesions in the posterior part of the hypothalamus also showed greatly impaired capacity to regulate against heat (Table 10). This is in part a confirmation and in part an extension of the observations of Teague and Ranson (1936).

It has been found that a region specifically responsive to heat exists above the chiasma and in the neighborhood of and below the anterior commissure. Heating of this region with a high frequency current led in over a pair of enameled nichrome wires causes panting and great increase in respiratory rate (Magoun, Harrison, Brobeck and Ranson, 1938). The results of the present investigation on the effects of lesions agree very well with those obtained by heating the brain if it is assumed that the "center" in the suprachiasmatic and preoptic region, which is sensitive to heat, sends fibers backward by way of the medial forebrain bundle in the lateral hypothalamus, which are interrupted by such lesions as those illustrated in Fig. 4, 5 and 6. It must be emphasized that although the suprachiasmatic and preoptic regions are sensitive to heat they do not contain the coordinating motor mechanism for panting, because decorticate polypneic panting can occur after these regions have been removed (Lilienthal and Otenasek, 1937). This motor mechanism occupies a more caudal position perhaps in the mesencephalon (Keller, 1933).

From the information at hand the most probable explanation of the transient hyperthermias seen in cats, monkeys (Ranson, Fisher and Ingram, 1937) and man after lesions in the anterior hypothalamus and the suprachiasmatic region is that these lesions cause an irritation of the centers for heat formation and heat conservation in the hypothalamus and that the resultant rise in temperature fails to activate the heat loss mechanism since the corresponding center has been destroyed or at least cut off from lower lying centers. Bilateral destruction of the caudal part of the lateral hypothalamus by large lesions

like those shown in Fig. 5 largely destroys the centers for heat formation and conservation and interrupts the descending paths from these centers as well as those from the center in the suprachiasmatic and preoptic region which is essential for regulation against heat. Such lesions cause a loss in the capacity to regulate against both heat and cold.

Summary

Large lesions in the hypothalamus in cats cause marked disturbances in temperature regulation and frequently result in the death of the animal. The farther back the hypothalamic lesions are placed the greater is the impairment of the ability to keep the body temperature up to the normal level and the more rapidly does death occur.

Large lesions in the region dorsal to the optic chiasma and ventral to the anterior commissure may cause serious impairment in the ability to prevent overheating without much disturbance in the ability to prevent chilling.

Bilateral lesions in the anterior part of the lateral hypothalamus cause a moderate impairment in the ability to prevent chilling and marked impairment in the ability to prevent overheating.

Bilateral lesions in the caudal part of the lateral hypothalamus have caused marked impairment in the ability to prevent both overheating and chilling.

Moderate sized medially placed lesions which do not invade the lateral hypothalamus have not caused much disturbance in temperature regulation irrespective of whether they were situated at the level of the infundibulum or at the level of the mammillary body.

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SIMILARITY OF EFFECTS OF BARBITURATE ANESTHESIA AND SPINAL TRANSECTION

H. K. BEECHER, F. K. McDONOUGH, AND A. FORBES
From the Surgical Laboratory of the Massachusetts General Hospital and the Department of Physiology of the Harvard Medical School, Boston

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DURING some recent studies of the influence of anesthetic agents upon the electrical activity in the cerebral cortex of cats, we used the flexion reflex, initiated by a series of induction shocks applied centrally to the sciatic nerve, as a rough measure of anesthetic depth. Under ether (Fig. 1, A, D), as in the decerebrate cat, a record of lower leg flexion shows a cumulative contractile effect. With a number of agents, notably the barbiturates, the character of the contractions was greatly altered (Fig. 1, B, C). In this case, scarcely any cumulative contraction occurred; rather, each stimulus was followed by isolated and approximately equal twitches, rising from and returning nearly to the base line. The similarity of these observations to those found by Forbes, Cobb and Cattell (1923) before and after low transection of the spinal cord, was obvious. The present study was planned to analyze this observation and to determine in what respects the effect of a barbiturate on the flexion reflex was similar to that of low spinal transection.

APPARATUS AND METHOD

Animals. Cats were used in all experiments, with artificial heating to maintain body temperature. For recording the flexion reflex, either the tibialis anticus or the hamstring muscles were used. Stimuli were applied to the central end of the severed sciatic nerve in the case of the hamstrings, and the popliteal nerve for tibialis anticus. The stimulating electrodes were silver wires mounted in a rubber tube. The stimulating apparatus consisted of a Harvard inductorium activated by a 1.5 volt dry cell and operated either by a mercury contact key manipulated by hand or by a rotary interrupter.

The time of stimulation was shown on the record by a string galvanometer signal device. The stimuli were single make or break induction shocks spaced from one to several seconds apart and followed by a rapid series of shocks (by hand). The strength of stimulus employed was that which would evoke approximately a maximal flexion reflex. When a rotary interrupter was used in the primary the frequency of stimulation, counting both makes and breaks, was from 7 to 10 per sec. For the *isotonic* preparation the writing lever was attached by cord to the ankle. Its excursions were restrained by an elastic band. The flexion response was recorded on a smoked drum. In order to obtain more faithful records of muscular contraction than is possible with the isotonic preparation, we used an *isometric* lever in several experiments. In the isometric preparation the hip joint of the cat was relatively immobilized by section of the femoral nerve, the psoas muscles and the glutei. The proximal and distal ends of the femur were pierced by drills. The leg was held fixed by inserting the drills into rigid clamps. Tibialis anticus was freed distally and a hitch of tendon taken about a steel hook. This was later applied to the torsion myograph described by Forbes, Davis and Lambert (1930). The sciatic nerve was dissected, and the branch to the hamstrings severed. The popliteal and peroneal divisions of the sciatic nerve were freed, and popliteal severed near the knee for stimulation. When the hamstring muscles were employed, essentially the same preparation was used, the nerve to this group being spared.

Muscle action currents. Freshly chlorided silver electrodes were inserted into tibialis anticus through small skin slits about one centimeter apart, at the mid-portion of the

muscle. Here also, the proximal lead was attached to the ground. The muscle electrodes were placed in circuit with the direct coupled amplifier described by Forbes and Grass (1937) connected with a string galvanometer. The potential changes between the leads were recorded on the same film as the myograph. A timer with 10 msec. units recorded on one margin of the film.

Nerve action currents. In an attempt to get further confirmatory evidence of the differences under the two agents, we recorded in several animals the action currents in the peroneal nerve, which appeared in response to stimulation of the popliteal. For this purpose the peroneal division of the sciatic nerve was severed near the knee and crushed one centimeter proximally to render the action currents monophasic. The nerve was placed in a moist chamber containing freshly chlorided electrodes. The proximal electrode was connected with the ground. The distal electrode (grid lead) supported the nerve between the cut end and the crushed area.

Anesthetics. Ether was administered by tracheal cannula. "Evipal" (1-methyl-5Δ' cyclohexenyl-5-methyl-barbituric acid) was administered either intravenously or intraperitoneally in doses of 10 to 40 mg. per kilo. The smaller doses were repeated at 10 to 30 minute intervals. This particular barbiturate was chosen because it is swiftly detoxified and recovery of the animal from its influence is relatively rapid. This made it possible to carry out a series of studies upon the same animal, alternating ether and "evipal" anesthesia. About 40 minutes were required for elimination of the ether after its administration was interrupted. If only very light "evipal" anesthesia was induced, the drug was rather completely destroyed in about this same length of time. While three alternations of agents were made in some cases, giving two series of observations under ether and two under "evipal" for comparison in the same animal, we found that the best data were obtained from the first ether and the first barbiturate observations.

RESULTS

Comparison of ether with barbiturates

Isotonic method. Typical examples of these effects are shown in Fig. 1; the four records were obtained in sequence in the same animal (stimuli induction shocks, by hand). In A, B, and C isolated shocks preceded the rapid series. In D the response to a rapid series alone is shown. Figure 1A was recorded at 2:56 p.m. under light ether anesthesia, the administration having previously been curtailed. Figure 1B was obtained at 3:20, 4 min. after a 30 mg. per

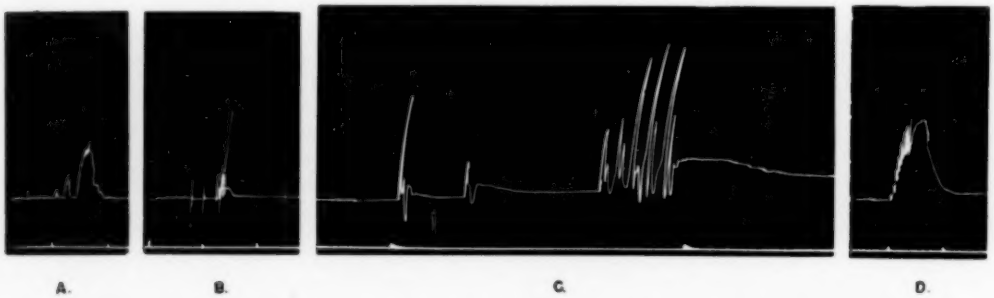

FIG. 1. Isotonic muscular contraction with flexion of the lower leg of the cat following induction shocks. Lower line, time in 5 sec. units. In A, B, and C 2 isolated shocks were followed by a rapid series; in D a rapid series only. A, under light ether anesthesia; B, later under light "evipal" anesthesia; C, the same as B with anesthesia a little lighter, fast drum; D shows resumption of typical ether response after return to that agent. A and D show the cumulative contraction under ether anesthesia. B and C show the discrete nature of the response found under a barbiturate ("evipal").

kilo dose of "evipal" had been administered. Figure 1C was observed at 3:26 and recorded on a fast drum, under somewhat lighter "evipal" anesthesia than was the case in B, as is indicated by the greater flexion response. Figure 1D was obtained at 5:14, 34 min. after ether anesthesia had been resumed (and 1 hr. and 58 min. since the barbiturate had been administered). This figure shows clearly the cumulative contraction under ether, on the one hand, and the isolated nature of the twitches under "evipal" on the other.

In a study of cortical action potentials under a considerable number of anesthetic agents in which the flexion reflex was used incidentally as a measure of depth of anesthesia, we have found the flexor response to be similar to that under ether [9] in the following*: nitrous oxide [4], ethylene [3], cyclopropane [4], chloroform [7], ethyl chloride [3], alcohol [4], amylene hydrate [3], trichlorethylene [4], urethane [4]. The following have yielded records like "evipal" [6], sodium barbital [4], "nembutal" [6], and chlorolosane [4]. The three barbiturates studied are examples of the so-called slow, moderate and fast acting barbiturates. It is probable that anesthesia by all members of this chemical family would result in the same alterations of the flexor response. The remainder have not fallen as clearly into the two groups. Whether the flexor response of these agents resembles the ether group or the barbiturate group seemingly depends upon the depth of anesthesia. In this intermediate group we have found tribromethanol [4], divinyl ether [4], and paraldehyde [4].

Isometric method. These are shown in Fig. 2, 3 and 4. Each figure was obtained from a different animal; the successive records of each figure were made chronologically from the same animal. In each case when one agent followed the other, ample time was allowed for the elimination of the ether or the destruction of the barbiturate. Figure 2 shows (preparation under ether anesthesia) the isometric response of tibialis anticus to induction shocks (by hand) at the rate of about 12 per sec., counting both makes and breaks, and of a strength to give approximately a maximal response on the break and a submaximal on the make. A brief protocol for Fig. 2 follows.

11:00 A.M.	Ether anesthesia started
1:00 P.M.	Record A obtained, under light ether anesthesia
1:15 P.M.	Ether anesthesia discontinued
1:20 P.M.	"Evipal" injected intravenously, 30 mg. per kilo body weight
2:37 P.M.	"Evipal" injected intravenously, 10 mg. per kilo body weight
2:45 P.M.	Record B obtained under deep "evipal" anesthesia
3:10 P.M.	Record C obtained under light "evipal" anesthesia
3:12 P.M.	Ether anesthesia resumed
3:43 P.M.	Record D obtained under moderately light ether anesthesia

It will be seen here, as in the case of the isotonic records, that this experiment also reveals a transition from sustained or cumulative contraction under ether, to isolated twitches under "evipal." It is noteworthy that with "evipal," even under deep anesthesia, the contractile response to each stimulus in the series appears as a larger excursion from the existing level than is the case during ether anesthesia.

Figure 3 shows (after preparation under "evipal") the typical barbiturate

* The number of experiments performed is indicated in brackets after each agent.

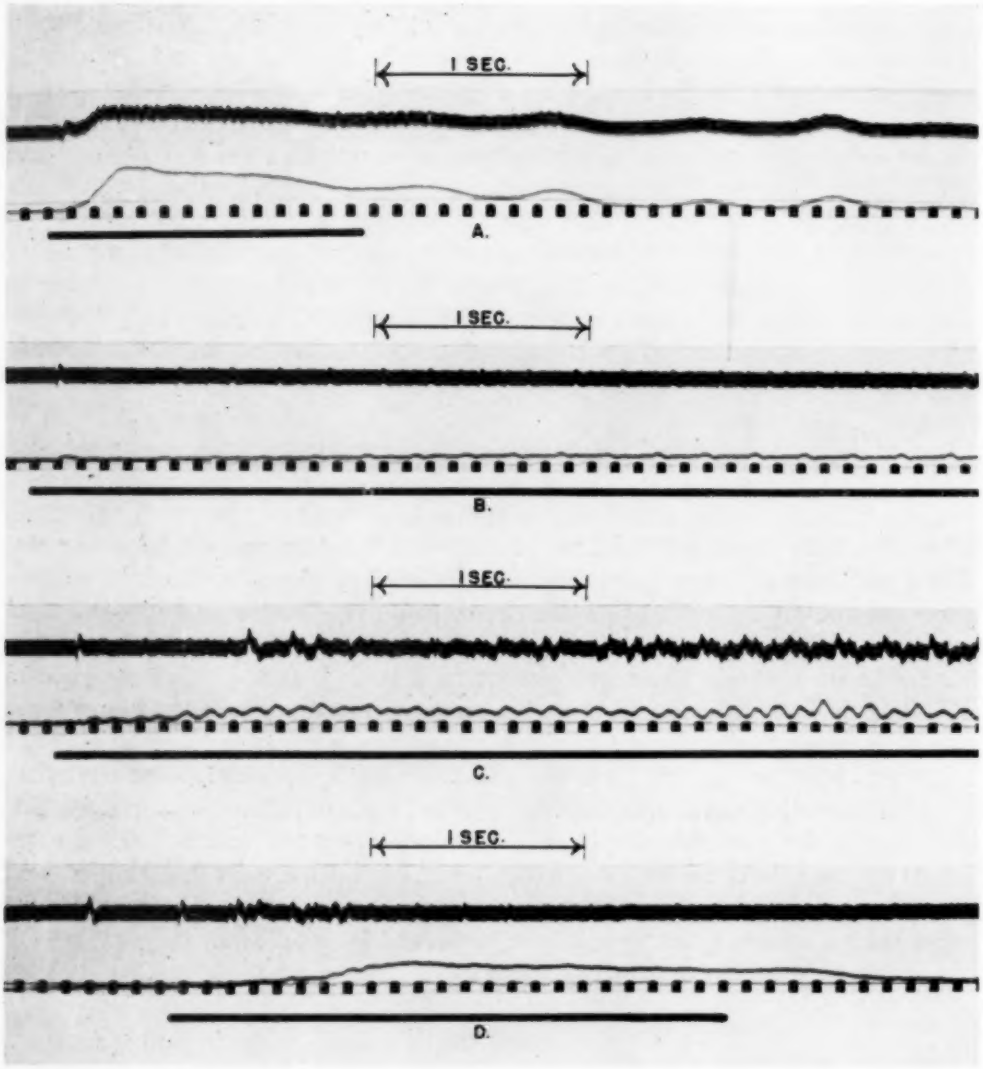

FIG. 2. Isometric contraction of tibialis anticus muscle (cat) in response to a series of induction shocks (by hand); preparation under ether anesthesia. Interval of stimulation is indicated by the solid line below the record, and the time unit is shown immediately above each record. Read from left to right. In all cases the upper tracing of each record represents the response of the galvanometer string to action currents in the muscle. An upward excursion of the string represents a negative potential of the proximal lead, in all cases unless otherwise specified. The lower tracing is that of the myogram: a rise in this signifies an increased muscle tension. A. 1 p.m. light ether anesthesia. B. 2:45 p.m. deep "evipal" anesthesia. C. 3:10 p.m. light "evipal" anesthesia. D. 3:43 p.m. moderately light ether anesthesia. The characteristic cumulative ether response is shown in A. The isolated, muscular twitches characteristic of a barbiturate are shown in B and C, while D shows, with the resumption of ether anesthesia, the return of the ether response.

isometric response of tibialis anticus to induction shocks (by hand) at the rate of about 5 per sec., counting only breaks. The breaks were approximately maximal in effect. A brief protocol for Fig. 3 follows.

1:45 P.M. "Evipal" administered intravenously, 30 mg. per kilo body weight
2:20 P.M. "Evipal" administered intravenously, 20 mg. per kilo body weight
3:25 P.M. "Evipal" administered intravenously, 10 mg. per kilo body weight
3:55 P.M. "Evipal" administered intravenously, 10 mg. per kilo body weight
4:25 P.M. Record A obtained under light "evipal" anesthesia
4:27 P.M. Ether anesthesia started
5:42 P.M. Record B obtained under light ether anesthesia

Here again, these records show the typical isolated twitches of the flexion response under "evipal" in contrast to the cumulative sweep found under ether. This figure shows even more strikingly than the preceding one (Fig. 2)

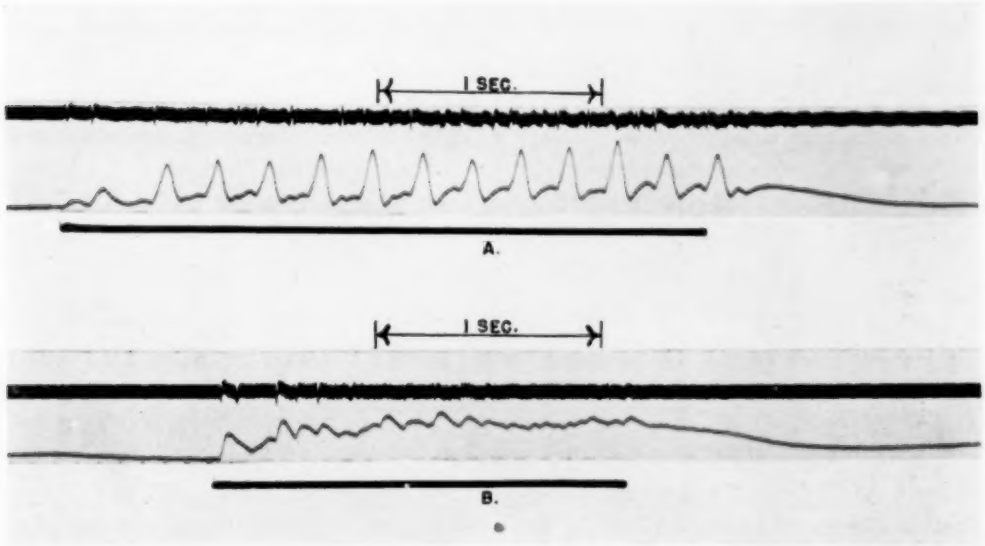

FIG. 3. Isometric contraction of tibialis anticus muscle in response to a series of induction shocks (by hand). Details are the same as for Fig. 2. Preparation under "evipal" anesthesia. A. 4:25 p.m. under light "evipal" anesthesia. B. 5:42 p.m. under light ether anesthesia.

the greater contractile effect of the individual twitches under "evipal" than under ether.

Figure 4 shows the response of the hamstring muscles (following an ether preparation) to induction shocks set up regularly by means of the rotary interrupter. The frequency of stimulation counting both makes and breaks was 10 per sec., in A and 8 in B. These shocks gave approximately a maximal muscle response. In this case, unlike the preceding, a downward excursion of the galvanometer string signifies negativity of the proximal lead. Ether anesthesia was started at 9:45 a.m. and maintained continuously until Record A was obtained at 1:23 p.m. The typical cumulative response of the flexion reflex under ether is shown. Ether administration was terminated at 1:20,

and 40 mg. per kilo. body weight of "evipal" were given intravenously at 1:27. Record B of Fig. 4, obtained at 2:11 p.m., shows the characteristic muscle response under a barbiturate.

The action current records of the *muscle* supplement the data by showing more clearly the more discrete responses under the barbiturate than under ether, in which often an irregular sequence of small excursions appears not correlated with the stimuli. In recording the *nerve* action currents we hoped to be able to demonstrate, in response to a rapid series of stimuli, a quick falling

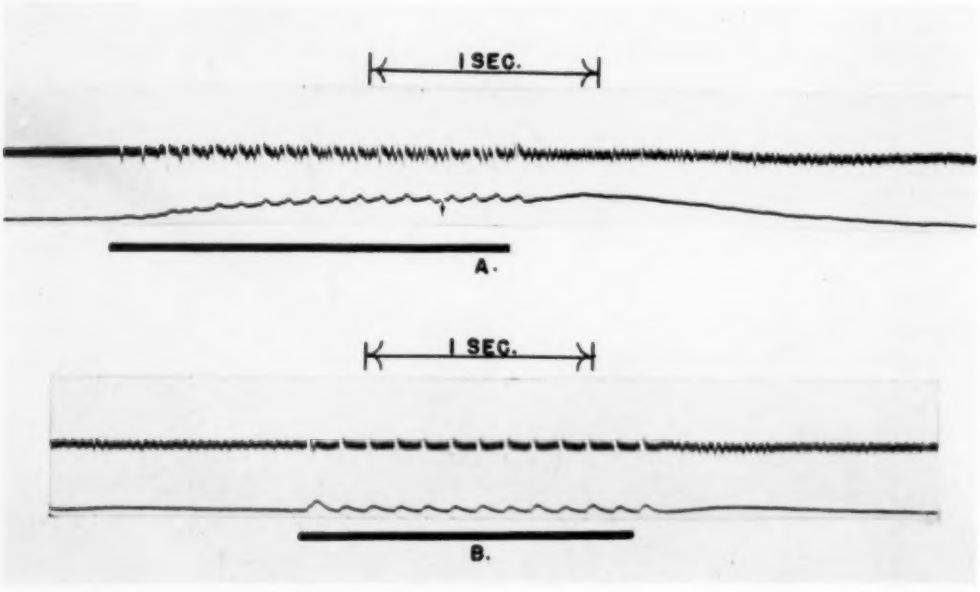

FIG. 4. Isometric contraction of the hamstring muscles in response to a series of induction shocks. Ether preparation. Details are the same as for Fig. 2 with the exception that here a downward excursion of the galvanometer string signifies negativity of the proximal grid lead. And also in this case, the induction shocks were spaced by a "rotary" interrupter. A. 1:23 p.m. ether anesthesia. B. 2:11 p.m. "evipal" anesthesia.

off in the size of the electric response, under ether anesthesia, and under the barbiturate a sustained amplitude of response, these effects being comparable to those found before and after spinal transection by Forbes and his associates (1923, 1929). In this attempt it was found impossible to compare responses under precisely comparable levels of anesthesia. In view of this the attempt was abandoned.

The figures demonstrate repeatedly both isotonically and isometrically the sustained cumulative contraction in the flexor response to stimuli under ether as contrasted with the relatively isolated twitches under the barbiturate "evipal." The similarity of the change in picture encountered in these experiments to that obtained by Forbes, Cobb and Cattell (1923) upon spinal transection at the level of the last rib is thus demonstrated. The outstanding

difference between the mechanical responses in the case of the two anesthetic agents appears to be the same as the difference arising from low transection of the spinal cord: namely, after transection, or under barbiturate anesthesia, the after-discharge is greatly reduced and the response to stimuli discrete, whereas, before transection, or under ether anesthesia, the relatively great after-discharge leads to a cumulative effect of a rapid series of stimuli and the curve of the response shows a sustained rise. These findings are in harmony with the conclusions of Bremer from his studies on a frog's spinal reflex (1934), and on the response of the cat's cerebral cortex to acoustic stimuli (1937).

The view is widely held (Forbes, 1922; Lorente de Nó, 1938) that after-discharge is due to internuncial neurones which, through long-circuiting of sensory impulses, provide for continued stimulation of the ventral horn cells after the original excitation has ceased. In the decerebrate animal and in the animal under ether the long-circuiting apparently is possible, but not so when the spinal cord is physically transected or the animal under the barbiturate anesthesia. One might infer, then, that the long-circuiting of sensory impulses is more greatly reduced under the barbiturate than under ether.

While attention has been drawn to the similarity of effects, it is not our intention to imply that the action of the barbiturates is similar to the effects of spinal transection in all respects. Doubtless many differences could be shown. In the features noted the changes are surprisingly alike and, we hope, offer data that may be of use in adding to the meager store of information concerning the site of action of various anesthetic agents.*

SUMMARY

The striking similarity of the effects of low spinal transection and barbiturate anesthesia upon the flexion reflex of the leg is reported. Isotonic and isometric muscle studies with muscle action currents have been used to demonstrate that under ether anesthesia a relatively sustained, cumulative reflex contraction of the leg flexors is regularly found upon repeated central stimulation of the sciatic nerve or its popliteal division; whereas, under barbiturate anesthesia ("evipal") *larger* isolated noncumulative twitches of the muscle occur in response to stimulation. The difference appears to be a matter of after-discharge, great in the case of ether, but little under barbiturate anesthesia. From this it is inferred that the "long-circuiting" of sensory impulses is much more seriously curtailed under barbiturate anesthesia than under ether. The behavior of the flexion reflex of the leg under 15 other anesthetic agents is reported.

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* The observations recorded here perhaps offer an explanation of the finding that the hind legs of dogs going under barbiturate anesthesia or recovering from it appear to be considerably more ataxic than the forelegs. On the other hand this phenomenon may be merely a demonstration of innate poorer coordination in the case of the hind legs.

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A STYLE BOOK CONTAINING SUGGESTIONS FOR THE PREPARATION OF MANUSCRIPTS

I. GENERAL DETAIL

Style and brevity

A WELL-KNOWN journal devoted to physiology has recently offered its contributors the following friendly advice: "Authors are asked to aim at writing papers as briefly as possible. Brevity, as a rule, accelerates publication, reduces editorial work and the cost of printing, and, lastly, lightens the burden of the reader. Errors from excessive brevity are more easily repaired than those from prolixity. It is important to remember that a reader's impression of a paper is often influenced by its literary style, and in his own interests the author should take pains about his style in order to convey his meaning to his readers. Care should be used in the choice of appropriate words and their place in the sentence, as well as in the sequence and linkage of sentences. A. P. Herbert's *What a Word!* and H. W. Fowlder's *Modern English Usage* may here be found helpful." To all this the editors of the *Journal of Neurophysiology* heartily subscribe.

In planning a paper material should be arranged, preferably with suitable headings, in the following order: (i) Introduction, stating the objects of the research and a brief history of the subject; (ii) Methods employed (in small print); (iii) Results, with illustrative protocols, diagrams or tables; (iv) Concise discussion; (v) Summary (preferably enumerated); (vi) Acknowledgments (small print); (vii) References; (viii) Legends for figures; (ix) Footnotes, when not typed in the body of the text; and finally (x) Illustrations with lettering complete.

Copy

The manuscript should be copied uniformly with *triple spacing* for parts to be printed in large type, with a margin of at least 1.25 inches (3 cm.) all around. The parts to be printed in small type should be typed on separate sheets in *double spacing*. The original typewritten copy should be packed flat for the mail or express. Corrections of the typescript should be typewritten or written legibly *in ink*. Manuscripts should be consistent in style; *i.e.*, a word should not be abbreviated on one page and written out on the next, nor temperature given in Fahrenheit in one place and Centigrade in another. Coöperation in making manuscripts as consistent as possible before submission for publication will greatly reduce editorial labor and the cost of alterations in the proof.

Preliminary matter

Title. The complete title of the paper in capitals together with the author's name(s) should appear on a *separate* first page; below this the institution

from which the paper emanates, the latter being underlined for italics. The usual arrangement is as follows:

THE POTASSIUM AND WATER CONTENTS OF CAT NERVES AS AFFECTED BY STIMULATION

WALLACE O. FENN

Department of Physiology, School of Medicine and Dentistry, The University of Rochester, Rochester, N. Y.

Running title. The second page of the manuscript should give an abbreviated form of the title, not exceeding 40 letters in length, to be used as a running headline, together with the exact address to which the proofs are to be sent. Any other special directions to the printer can be included on this page.

Headings

Major headings, such as INTRODUCTION, METHODS, DISCUSSION, SUMMARY and REFERENCES are printed in capitals. Minor headings, whether center or side, and descriptive matter in table headings, are printed in italics and therefore should be underlined *once*.

Text

The text (including center headings) should be typed on consecutive pages until; (i) an experiment, (ii) a protocol, (iii) a table, (iv) a description of technical procedures, (v) a quotation of over five lines, (vi) a formula or equation, or (vii) description of technical procedure. *Begin every experiment, protocol, table, description of technical procedure, quotation of over five lines, formula, equation, or technical procedure, on a new page, regardless of where the preceding text ends on the page.* After the experiment or table, etc., has been copied on one or more sheets, proceed with the text on a new sheet until the next experiment or table, etc., is reached, when the same procedure is repeated.

This method brings the material of the entire manuscript in sequence, but permits, without mutilation of the manuscript, the separation in the printer's office of tables, and all other small type, which are set up separately by hand or on separate monotype machines. *Authors are requested to mark in the margin those portions of the paper that should be printed in small type.* The sheets should be numbered consecutively throughout, with the place of insertion of each text-figure indicated on the copy in ink. In the text, tables and figures should always be referred to specifically by number, *i.e.*, Fig. 2, not "the following figure." It is obviously not always possible to insert a table or figure in the precise place requested when the paper is arranged in page form.

Spelling

All preferences of spelling and literary usage will be respected unless the manuscript is inconsistent; minor deviations will be corrected in the editorial office. Major editorial changes will ordinarily be submitted to the author.

Footnotes

Footnotes should be typed in single space, numbered consecutively throughout the text and preferably inserted immediately after the line of text which requires the footnote, no matter where it occurs on the page.

References

Verification of references. The *Journal* office takes care of reading the page proof, but can not verify references; responsibility for this must rest entirely with the author. Since references are useless unless correct, authors are urged to verify against the source every reference after it has been transcribed so that it may be complete and correct in each detail—spelling, especially of proper names and foreign titles, journals, date, volume number, page numbers, punctuation and, above all, accents.

Form. Three systems may be adopted for the arrangement of references: (i) The references are arranged and numbered in the order of their appearance in the text, (ii) or arranged alphabetically according to the name of the author, the text reference being the name of the author with the year of publication referred to or (iii) the alphabetically arranged list numbered consecutively. Manuscripts will be returned if references are not in correct form and complete. Text references are indicated by an exponential number or by date.

Form of citation. The form of citation for *journals* is indicated by the following example:

(i) SHERRINGTON, C. S. Decerebrate rigidity, and reflex coordination of movements. *J. Physiol.*, 1898, *22:* 319–332.

Citations of *books* follow the same procedure except that for single volumes the total pagination should be indicated so that the extent of the book is obvious, for example:

(ii) MAGNUS, R. *Körperstellung.* Berlin, J. Springer, 1924, xiii, 740 pp.

When a book is two or more volumes, total pagination is unnecessary as in the following:

(iii) RAMÓN Y CAJAL, S. *Histologie du système nerveux de l'homme et les vertébrés.* Paris, Maloine, 1909–1911, 2 vols.

Handbooks and special serials can be treated in the manner of a journal, *e.g.*,

(iv) FOERSTER, O. Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln. *Bumke u. Foersters Handb. Neurol.*, 1936, *6:* 1–448.

(v) BROUWER, B. Certain aspects of the anatomical basis of the phylogeny of encephalization. *Res. Publ. Ass. nerv. ment. Dis.*, 1934, *13:* 3–25.

In all citations authors' names should be in capitals, followed by the title of the paper, journal (abbreviated, see below) underlined once, year, volume (arabic numerals) underlined once, initial and final pages (see example i). In the case of books the authors' names should likewise be in capitals, followed by the title underlined once, place of publication, publisher, date and

total number of pages or volumes (see examples ii and iii). Reference to a specific page should be included when the citation is mentioned in the text (thus, Parker, 1918, p. 216).

The journal abbreviations should be in accordance with the system used in *A word list of scientific periodicals published in the years 1900–1933*, 2nd ed., (London and New York, Oxford University Press, 1934.) A list of the abbreviated titles of journals frequently cited in neurophysiological work is given on pp. 93–99.

Illustrations

All illustrations, especially photographs, should be sharp, of clear and submitted ready for reproduction, *i.e.*, with *professional lettering*, mounting and arrangements of figures completed. *Each illustration must have printed on the back author's name, address and the figure number.* If the original of a figure is submitted, it is hoped that the author will also include a photograph for editorial use. This will mimimize the danger of loss or injury to an original (*e.g.*, kymograph record).

II. LIST OF USUAL ABBREVIATIONS*

Absolute	abs.	Henry	H.
Absolute degrees	°K.	Horse power	H.P.
Alternating current	A.C.	Hour	hr. (but m.p.h.)
Ampere	A.		
Ångstrom unit (10^{-8} cm.)	Å.	Hydrogen ion concentration (negative logarithm of)	pH
Arterial pressure	A.P.		
Atmosphere	atm.	Kilogram	kg.
Atomic weight	at. wt.	Kilogram meter	kg.m.
Blood pressure	B.P.	Kiloliter	kl.
Boiling point	b.p.	Kilometer	km.
British Thermal Unit	B.TH.U.	Kilovolt	kV.
Calculated (in table headings)	calc.	Kilovolt ampere	kVA.
Calorie (large)	kcal.	Kilowatt	kW.
Calorie (small)	cal.	Liter	l.
Candle	c.	Maximum	max.
Candle power	C.P.	Megacycle per second	Mc./sec.
Centigrade	C.	Megohm	MΩ. or MO.
Centimeter	cm.	Melting point	M.P.
Cubic centimeter	cc.	Meter	m.
Cubic millimeter	c.mm.	Micron (10^{-3} mm. = 10^{-6} m.)	μ.
Cubic (other than in cc. and c.mm.)	cu.	Millimicron (10^{-6} mm.)	mμ.
		Micromicron (10^{-9} mm.)	μμ.
Cycles per second	c./sec.	Microampere	μA.
Direct current	D.C.	Microgram	μg.
Electromotive force	E.M.F.	Micromilligram	μmg.
Fahrenheit	F.	Micromicrogram (10^{-12} gram)	μμg.
Farad	F.	Microfarad	μF.
Figure	Fig.	Microhenry	μH.
Fractions	0.1	Micromicrofarad	μμF.
Gamma (10^{-3} mg.)	γ	Microsecond	μsec.
Gram	g.	Microvolt	μV.
Gravity, accleration due to	*g*	Milliampere	mA.

* Compiled from accepted international conventions.

Milligram	mg.	Page, pages	p. pp.
Millihenry	mH.	per cent	per cent
Milliliter	ml.	Potential difference	P.D.
Millimeter	mm.	Revolutions per minute	rev./min.
Millimicron	$m\mu$	Second (time)	sec.
Millisecond (sigma)	msec.	Sigma (10^{-3} sec.)	σ
Millivolt	mV.	Specific gravity	sp. gr.
Milliwatt	mW.	Specific heat	sp. ht.
Minute (time)	min.	Square (*e.g.* sq. cm.)	sq.
Molar	*M*	Temperature (in table headings)	temp.
Molecule or Molecular	mol.	Time	a.m., p.m.
Normal (of solution)	*N*	Venous pressure	V.P.
1/10th normal	0.1 *N*	Volume	vol.
1/100th normal	0.01 *N*	Volt	V.
Normal temperature and pressure	N.T.P.	Watt	W.
Observed (in table headings)	obs.	Wave-length	λ
Ohm	Ω. or O.		

III. LIST OF PERIODICALS AND THEIR ABBREVIATIONS

*The abbreviations follow those of the World list of scientific periodicals**

PERIODICAL	ABBREVIATION
Abhandlungen der Kgl. Sächsischen Gesellschaft (Akademie der Wissenschaften. Math.-Phys. Kl.) Leipzig	Abh. sachs. Ges. (Akad.) Wiss.
Acta chirurgica Scandinavica	Acta chir. scand.
Acta medica Scandinavica	Acta med. scand.
Acta obstetrica et gynecologica Scandinavica	Acta obstet. gynec. scand.
Acta opthalmologica	Acta ophthal., Kbh.
Acta oto-laryngologica	Acta oto-laryng. Stockh.
Acta psychiatrica et neurologica	Acta psychiat., Kbh.
Acta Scholae medicinalis Universitatis Imperialis in Kioto	Acta Sch. med. Univ. Kioto
Alexander und Marburgs, Handbuch der Neurologie des Ohres	Handb. Neurol. Ohres
American Journal of Anatomy	Amer. J. Anat.
American Journal of Diseases of Children	Amer. J. Dis. Child.
American Journal of Hygiene	Amer. J. Hyg.
American Journal of the Medical Sciences	Amer. J. med. Sci.
American Journal of Obstetrics and Gynaecology	Amer. J. Obstet. Gynaec.
American Journal of Pathology	Amer. J. Path.
American Journal of Pharmacy	Amer. J. Pharm.
American Journal of Physiology	Amer. J. Physiol.
American Journal of Psychiatry	Amer. J. Psychiat.
American Journal of Psychology	Amer. J. Psychol.
American Journal of Tropical Diseases	Amer. J. trop. Dis.
Anatomical Record	Anat. Rec.
Anatomischer Anzeiger	Anat. Anz.
Annalen der Chemie	Liebigs Ann.
Annalen der Physik	Ann. Phys., Lpz.
Annales de Chimie (et de Physique)	Ann. Chim. (Phys.)
Annales de l'Institut Pasteur	Ann. Inst. Pasteur
Annales de Médecine	Ann. Méd.

* *A world list of scientific periodicals published in the years 1900–1933.* 2nd edition London and New York: Oxford University Press, 1934. xiv, 780 pp.

Annales de Physiologie et de Physicochimie	Ann. Physiol. Physicochim. biol.
Annales de Physique	Ann. Phys., Paris
Annales de la Société Royale des sciences médicales et naturelles de Bruxelles	Ann. Soc. Sci. méd. nat. Brux.
Annali d'Igiene (sperimentale)	Ann. Igiene (sper.)
Annals of Applied Biology	Ann. appl. Biol.
Annals of Internal Medicine	Ann. intern. Med.
Arbeiten aus d. neurologischen Institut (Inst. f. Anatomie u. Physiologie d. Zentralnervensystems) an der Wiener Universität	Arb. neurol. Inst. (Inst. Anat. Physiol. ZentNerv.) Univ. Wien
Arbeitsphysiologie	Arbeitsphysiologie
Archiv für Anatomie und Pharmakologie	Arch. Anat. Pharmak.
Archiv für Anatomie und Physiologie	Arch. Anat. Physiol., Lpz.
Archiv für Augenheilkunde	Arch. Augenheilk.
Archiv für Entwicklungsmechanik der Organismen	Arch. EntwMech. Org.
Archiv für experimentelle Pathologie und Pharmakologie	Arch. exp. Path. Pharmak.
Archiv für die gesamte Physiologie	Pflüg. Arch. ges. Physiol.
Archiv für Gynaekologie	Arch. Gynaek.
Archiv für Hygiene	Arch. Hyg., Berl.
Archiv für mikroskopische Anatomie	Arch. mikr. Anat.
Archiv für Ophthalmologie	v. Graefes Arch. Ophthal.
Archiv für pathologische Anatomie	Virchows Arch.
Archiv für Psychiatrie und Nervenkrankheiten	Arch. Psychiat. Nervenkr.
Archiv für Verdauungskrankheiten	Arch. VerdauKr.
Archives de Biologie	Arch. Biol., Paris
Archives of Internal Medicine	Arch. intern. Med.
Archives internationales de Pharmacodynamie (et de Thérapie)	Arch. int. Pharmacodyn.
Archives internationales de Physiologie	Arch. int. Physiol.
Archives italiennes de Biologie	Arch. ital. Biol.
Archives de médecine expérimentale et d'anatomie pathologique	Arch. Méd. exp.
Archives néerlandaises de Physiologie	Arch. néerl. Physiol.
Archives de Neurologie	Arch. Neurol., Paris
Archives of Neurology and Psychiatry, Chicago	Arch. Neurol. Psychiat., Chicago
Archives of Neurology and Psychiatry, London	Arch. Neurol. Psychiat., Lond.
Archives d'Ophtalmologie	Arch. Ophtal., Paris
Archives of Ophthalmology	Arch. Ophthal., N.Y.
Archives de Physiologie normale et pathologique	Arch. Physiol. norm. path.
Archives des Sciences biologiques	Arch. Sci. biol.
Archivio di farmacologia sperimentale e scienze affini	Arch. Farmacol. sper.
Archivio di Fisiologia	Arch. Fisiol.
Archivio per le Scienze mediche	Arch. Sci. med.
Association for Research in Nervous and Mental Disease Publications	Res. Publ. Ass. nerv. ment. Dis.
Atti della R. Accademia dei Lincei (Memorie)	Mem. Accad. Lincei
Atti della R. Accademia dei Lincei (Rendiconti)	R.C. Accad. Lincei
Atti della R. Accademia delle Scienze di Torino	Atti Accad. Torino
Atti del R. Istituto veneto di scienze, lettere ed arti	Atti Ist. veneto
Atti della Società lombarda di Scienze mediche e biologiche	Atti Soc. lombarda Sci. med. biol.
Australian Journal of Experimental Biology and Medical Science	Aust. J. exp. Biol. med. Sci.
Beiträge zur chemischen Physiologie und Pathologie	Beitr. chem. Physiol. Path.
Beiträge zur Geburtshilfe und Gynäkologie	Beitr. Geburtsh. Gynäk.
Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie	Beitr. path. Anat.
Bericht der deutschen chemischen Gesellschaft	Ber. dtsch. chem. Ges.

Bericht über die gesamte Physiologie und experimentelle Pharmakologie	Ber. ges. Physiol.
Berliner klinische Wochenschrift	Berl. klin. Wschr.
Bethes Handbuch der normalen und pathologischen Physiologie	Handb. norm. path. Physiol.
Bibliothek for Laeger	Bibl. Laeger
Biochemical Journal	Biochem. J.
Biochemische Zeitschrift	Biochem. Z.
Biological Bulletin of the Marine Biological Laboratory, Wood's Hole	Biol. Bull. Wood's Hole
Biological Reviews	Biol. Rev.
Biologisches Zentralblatt	Biol. Zbl.
Bolletino della Società italiano di biologia sperimentale	Boll. Soc. ital. Biol. sper.
Brain	Brain
British Journal of Children's Diseases	Brit. J. Child. Dis.
British Journal of Experimental Biology	Brit. J. exp. Biol.
British Journal of Experimental Pathology	Brit. J. exp. Path.
British Journal of Ophthalmology	Brit. J. Ophthal.
British Journal of Psychology	Brit. J. Psychol.
British Medical Journal	Brit. med. J.
Bulletin de l'Académie de Médecine de Belgique	Bull. Acad. Méd. Belg.
Bulletin de l'Académie de Médecine de Paris	Bull. Acad. Méd. Paris
Bulletin biologique de la France et de la Belgique	Bull. biol.
Bulletin of the Neurological Institute of New York	Bull. neurol. Inst. N.Y.
Bulletin of the New York Academy of Medicine	Bull. N.Y. Acad. Med.
Bulletin et mémoires de la Société anatomique de Paris	Bull. Soc. anat. Paris
Bulletin et mémoires de la Société médicale des hôpitaux de Paris	Bull. Soc. méd. Hôp. Paris
Bulletin de la Société de Chimie biologique	Bull. Soc. Chim. biol. Paris
Bumke und Foersters Handbuch der Neurologie	Bumke u. Foersters Handb. Neurol.
Canadian Medical Association Journal	Canad. med. Ass. J.
Carnegie Institution of Washington Publications	Publ. Carneg. Instn.
Cellule	Cellule
Chemical Abstracts	Chem. Abstr.
Chemische Zeitschrift	Chem. Z.
Chinese Journal of Physiology	Chin. J. Physiol.
Chinese Journal of Physiology. Report Series	Chin. J. Physiol. Rep. Ser.
Clinical Science	Clin. Sci.
Cold Spring Harbor Monographs	Cold Spr. Harb. Monogr.
Comptes rendus hebdomadaires des séances de l'Acad. des Sciences	C.R. Acad. Sci., Paris
Comptes rendus hebdomadaires des séances et mémoires de la Société de Biologie	C.R. Soc. Biol., Paris
Confinia Neurologica	Conf. neurol.
Congrès international de neurologie, de psychiatrie (et de psychologie)	Congr. int. Neurol. Psychiat. (Psychol.)
Deutsche medizinische Wochenschrift	Dtsch. med. Wschr.
Deutsche Zeitschrift für Nervenheilkunde	Dtsch. Z. Nervenheilk.
Encéphale	Encéphale
Endocrinology	Endocrinology
Endokrinologie	Endokrinologie
Ergebnisse der Physiologie	Ergebn. Physiol.
Fermentforschung	Fermentforschung
Folia anatomica japonica	Folia anat. japon.

Folia haematologica	Folia haemat.
Folia neuro-biologica. Leipzig	Folia neuro-biol. Lpz.
Fortschritte der Neurologie und Psychiatrie	Fort. Neur. Psychiat.
Gegenbaurs morphologisches Jahrbuch	Gegenbaurs Jb.
Giornale di biologia e medicina sperimentale	G. Biol. Med. sper.
Graefes Archiv	v. Graefes Arch. Ophthal.
Guy's Hospital Reports	Guy's Hosp. Rep.
Haematologica	Haematologica
Handbuch der Biochemie (Oppenheimer)	Handb. Biochem. Berl.
Handbuch der biochemischen Arbeitsmethoden	Handb. boichem. ArbMeth.
Handbuch der Neurologie des Ohres (Alexander and Marburg)	Handb. Neurol. Ohres
Handbuch der Neurologie (Bumke und Foerster)	Bumke u. Foersters Handb. Neurol.
Handbuch der Neurologie (Lewandowsky)	Lewandowskys Handb. Neurol.
Handbuch der normalen und pathologischen Physiologie (Bethe)	Handb. norm. path. Physiol.
Handbuch der Physiologie (Hermann)	Handb. Physiol.
Handbuch der vergleichenden Physiologie	Handb. vergl. Physiol.
Harvey Lectures	Harv. Lect.
Heart	Heart
Hermanns Handbuch der Physiologie	Handb. Physiol.
Hoppe-Seylers Zeitschrift f. physiologische Chemie	Hoppe-Seyl. Z.
Indian Journal of Medical Research	Ind. J. med. Res.
International Congress of Experimental Psychology	Int. Congr. exp. Psychol.
International Physiological Congress	Int. physiol. Congr.
Internationale Monatsschrift f. Anatomie und Physiologie	Int. Mschr. Anat. Physiol.
Jahrbuch für Psychiatrie und Neurologie	Jb. Psychiat. Neurol.
Jahresbericht Physiologie und experimentelle Pharmakologie	Jber. Physiol. exp. Pharm.
Japanese Journal of Medical Sciences	Jap. J. med. Sci.
Part 2. Biochemistry	Biochem.
Part 3. Biophysics	Biophys.
Johns Hopkins Hospital Bulletin	Johns Hopk. Hosp. Bull.
Johns Hopkins Hospital Reports	Johns Hopk. Hosp. Rep.
Journal of the American Chemical Society	J. Amer. chem. Soc.
Journal of the American Medical Association	J. Amer. med. Ass.
Journal de l'Anatomie et de la Physiologie	J. Anat., Paris
Journal of Anatomy	J. Anat., Lond.
Journal of Bacteriology	J. Bact.
Journal belge de Neurologie et Psychiatrie	J. belge Neurol. Psychiat.
Journal of Biochemistry	J. Biochem.
Journal of Biological Chemistry	J. biol. Chem.
Journal of Biophysics	J. Biophys., Tokyo
Journal of Cellular and Comparative Physiology	J. cell. comp. Physiol.
Journal of Clinical Investigation	J. clin. Invest.
Journal of Comparative Neurology	J. comp. Neurol.
Journal of Comparative Psychology	J. comp. Psychol.
Journal of Experimental Biology	J. exp. Biol.
Journal of Experimental Medicine	J. exp. Med.
Journal of Experimental Psychology	J. exp. Psychol.
Journal of Experimental Zoology	J. exp. Zool.
Journal of General Physiology	J. gen. Physiol.
Journal of General Psychology	J. gen. Psychol.
Journal of Genetics	J. Genet.
Journal of Hygiene	J. Hyg., Camb.

Journal of Infectious Diseases	J. infect. Dis.
Journal of Laboratory and Clinical Medicine	J. Lab. clin. Med.
Journal of the Marine Biological Association	J. Mar. biol. Ass. U.K.
Journal of Medical Research	J. med. Res.
Journal of Mental Science	J. ment. Sci.
Journal of Metabolic Research	J. metab. Res.
Journal of Nervous and Mental Diseases	J. nerv. ment. Dis.
Journal de Neurologie	J. Neurol. Brux.
Journal of Neurology and Psychopathology	J. Neurol. Psychopath.
Journal of Neurophysiology	J. Neurophysiol.
Journal of Nutrition	J. Nutrit.
Journal of Obstetrics and Gynaecology	J. Obstet. Gynaec.
Journal of the Optical Society of America	J. opt. Soc. Amer.
Journal of Pathology and Bacteriology	J. Path. Bact.
Journal de Pharmacie et de Chimie	J. Pharm. Chim., Paris
Journal of Pharmacology and Experimental Therapeutics	J. Pharmacol.
Journal de Physiologie et de Pathologie générale	J. Physiol. Path. gén.
Journal of Physiology	J. Physiol.
Journal für Psychologie und Neurologie	J. Psychol. Neurol., Lpz.
Journal de Psychologie normale et pathologique	J. Psychol. norm. path.
Journal of Psychology	J. Psychol., Provincetown
Journal of the Royal Microscopical Society	J. R. micr. Soc.
Journal of Scientific Instruments	J. sci. Instrum.
Journal of Washington Academy of Sciences	J. Wash. Acad. Sci.
Klinische Monatsblätter für Augenheilkunde	Klin. Mbl. Augenheilk.
Klinische Wochenschrift	Klin. Wschr.
Kolloidzeitschrift	Kolloidzschr.
Lancet	Lancet
Lewandowskys Handbuch der Neurologie	Lewandowskys Handb. Neurol.
Liebigs Annalen der Chemie	Liebigs Ann.
Medical Journal of Australia	Med. J. Aust.
Medical Journal of South Africa	Med. J. S. Afr.
Medical Science, Abstracts and Reviews	Med. Sci.
Medico-Chirurgical Transactions	Med.-chir. Trans.
Mémoires couronnés et autres mémoires p.p. l'Académie R. de médecine de Belgique	Mém. cour. Acad. Méd. Belg.
Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie	Mitt. Grenzgeb. Med. Chir.
Monatsschrift für Kinderheilkunde	Mschr. Kinderheilk.
Monatsschrift für Ohrenheilkunde u. Laryngologie	Mschr. Ohrenheilk.
Monatsschrift für Psychiatrie und Neurologie	Mschr. Psychiat. Neurol.
Monitore zoologico italiano	Monit. zool. ital.
Morgagni	Morgagni
Morphologisches Jahrbuch	Morph. Jb.
Münchener medizinische Wochenschrift	Münch. med. Wschr.
Nature	Nature, Lond.
Naturwissenschaften	Naturwissenschaften
Nederlandsch Tijdschrift voor Geneeskunde	Ned. Tijdschr. Geneesk.
Nervenarzt	Nervenarzt
Neurological Bulletin	Neurol. Bull.
Neurologisches Zentralblatt	Neurol. Zbl.
Névraxe	Névraxe
New England Journal of Medicine	New Engl. J. Med.
Oppenheimers Handbuch der Biochemie	Handb. Biochem., Berl.

Pflügers Archiv für die gesamte Physiologie	Pflüg. Arch. ges. Physiol.
Philosophical Magazine	Phil. Mag.
Philosophical Transactions of the Royal Society	Philos. Trans.
Physikalische Zeitschrift	Phys. Z.
Physiological Abstracts	Physiol. Abstr.
Physiological Reviews	Physiol. Rev.
Policlinico	Policlinico
Presse médicale	Pr. méd.
Proceedings of the National Academy of Sciences, Washington	Proc. nat. Acad. Sci., Wash.
Proceedings of the Physiological Society	Proc. Physiological Soc.
Proc. of the Royal Academy of Sciences Amsterdam	Proc. Acad. Sci. Amst.
Proceedings of the Royal Dublin Society	Sci. Proc. R. Dublin Soc.
Proceedings of the Royal Society	Proc. roy. Soc.
Proceedings of the Royal Society of Canada	Proc. roy. Soc. Can.
Proceedings of the Royal Society of Edinburgh	Proc. roy. Soc. Edinb.
Proceedings of the Royal Society of Medicine	Proc. R. Soc. Med.
Proceedings of the Society of Experimental Biology and Medicine	Proc. Soc. exp. Biol., N.Y.
Proceedings of the Zoological Society London	Proc. zool. Soc. Lond.
Psychiatrische en neurologische bladen, Amsterdam	Psychiat. neurol. Bl., Amst.
Psychiatric Quarterly	Psychiat. Quart.
Psychological Monographs	Psychol. Monogr.
Psychological Rev.	Psychol. Rev.
Pubblicazioni della Stazione zoologica di Napoli	Pubbl. Staz. zool. Napoli
Quarterly Journal of Experimental Physiology	Quart. J. exp. Physiol.
Quarterly Journal of Medicine	Quart. J. Med.
Quarterly Journal of Microscopical Science	Quart. J. micr. Sci.
Quarterly Journal of Pharmacy and Allied Sciences	Quart. J. Pharm.
Quarterly Review of Biology	Quart. Rev. Biol.
Rendiconti della R. Accademia dei Lincei	R.C. Accad. Lincei
Reports of British Association	Rep. Brit. Ass.
Research Publications Association for Research in Nervous and Mental Disease	Res. Publ. Ass. nerv. ment. Dis.
Revue française d'endocrinologie	Rev. franç. Endocrin.
Revue neurologique	Rev. neurol.
Riforma Medica	Rif. med.
Rivista di biologia	Riv. biol.
Science	Science
Science Abstracts	Sci. Abstr.
Scientific Proceedings of the Royal Dublin Society	Sci. Proc. R. Dublin Soc.
Schweizer Archiv für Neurologie und Psychiatrie	Schweiz. Arch. Neurol. Psychiat.
Sitzungsberichte der Akademie der Wissenschaften in Wien	S.B. Akad. Wiss. Wien
Abt. III Anatomie und Physiologie	Anat. Physiol.
Sitzungsberichte der Kgl. preussischen Akademie der Wissenschaften z. Berlin	S. B. preuss. Akad. Wiss.
Skandinavisches Archiv für Physiologie	Skand. Arch. Physiol.
South African Journal of Science	S. Afr. J. Sci.
Special Report Series Medical Research Council London	Spec. Rep. Ser. med. Res. Coun., Lond.
Sperimentale. Archivio di biologia normale e patologica	Sperimentale
Stanford University Publications—University Series	Stanford Univ. Publ.
Biological Sciences	biol. Sci.
Medical Sciences	med. Sci.
Surgery, Gynecology and Obstetrics	Surg. Gynec. Obstet.

Tabulae biologicae	Tabul. biol., Berl.
Tohoku Journal of Experimental Medicine	Tohoku J. exp. Med.
Transactions of the Faraday Society	Trans. Faraday Soc.
Transactions of the Optical Society	Trans. opt. Soc. Lond.
Transactions of the Royal Society of Canada	Trans. Roy. Soc. Can.
Transactions of the Royal Society of Edinburgh	Trans. Roy. Soc. Edinb.
Transactions of the Royal Society of South Africa	Trans. Roy. Soc. S. Afr.
Transactions of the Zoological Society	Trans. zool. Soc. Lond.
Travaux du Laboratoire des recherches biologiques de l'Université de Madrid	Trab. Lab. Invest. biol. Univ. Madr.
Ugeskrift för Laeger	Ugeskr. Laeg.
University of California Publications	Univ. Calif. Publ.
Verhandelingen der (Kon.) Akad. van Wetenschappen	Verh. Akad. Wet., Amst.
Verhandelungen der anatomischen Gesellschaft	Verh. anat. Ges. Jena
Verhandelungen der Deutschen Gesellschaft der innere Medizin	Verh. dtsch. Ges. inn. Med.
Verhandelungen der Gesellschaft deutscher Nervenärzte	Verh. Ges. dtsch. Nervenärz.
Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin	Virchows Arch.
Wiener klinische Wochenschrift	Wien klin. Wschr.
Wiener medizinische Wochenschrift	Wien. med. Wschr.
Zeitschrift für allgemeine Physiologie	Z. allg. Physiol.
Zeitschrift für Augenheilkunde	Z. Augenheilk.
Zeitschrift für Biologie	Z. Biologie
Zeitschrift für experimentelle Pathologie und Therapie	Z. exp. Path. Ther.
Zeitschrift für die gesamte Anatomie	Z. ges. Anat.
Zeitschrift für die gesamte experimentelle Medizin	Z. ges. exp. Med.
Zeitschrift für die gesamte Neurologie und Psychiatrie	Z. ges. Neurol. Psychiat.
Zeitschrift für Hygiene und Infektionskrankheiten	Z. Hyg. InfektKr.
Zeitschrift für Immunitätsforschung	Z. ImmunForsch.
Zeitschrift für Kinderheilkunde	Z. Kinderheilk.
Zeitschrift für klinische Medizin	Z. klin. Med.
Zeitschrift für Kreislaufforschung	Z. KreislForsch.
Zeitschrift für die medizinische Wissenschaften	Z. med. Wiss.
Zeitschrift für mikroskopisch-anatomische Forschung	Z. mikr.-anat. Forsch.
Zeitschrift für physikalische Chemie	Z. phys. Chem.
Zeitschrift für physiologische Chemie	Hoppe-Seyl. Z.
Zeitschrift für Psychologie und Physiologie der Sinnesorgane	Z. Psychol. Physiol. Sinnesorg.
Zeitschrift für Sinnesphysiologie	Z. Sinnesphysiol.
Zeitschrift für vergleichende Physiologie	Z. vergl. Physiol.
Zeitschrift für wissenschaftliche Zoologie	Z. wiss. Zool.
Zeitschrift für Zellforschung und mikroskopische Anatomie	Z. Zellforsch.
Zentralblatt für Biochemie und Biophysik	Zbl. Biochem. Biophys.
Zentralblatt für die gesamte Gynäkologie und Geburtshilfe	Zbl. ges. Gynäk. Geburtsh.
Zentralblatt für die gesamte Neurologie und Psychiatrie	Zbl. ges. Neurol. Psychiat.
Zentralblatt für medizinische Wissenschaften	Zbl. med. Wiss.
Zentralblatt für Nervenheilkunde	Zbl. Nervenheilk.
Zentralblatt für Physiologie	Zbl. Physiol.